T.R. MINISTRY of HEALTH
GENERAL DIRECTORATE OF
PUBLIC HEALTH

TURKEY CANCER CONTROL PROGRAMME

T.R. MINISTRY of HEALTH
GENERAL DIRECTORATE OF
PUBLIC HEALTH

TURKEY
CANCER CONTROL PROGRAMME

ANKARA 2021

Publishing Coordinators

Assoc. Prof. Dr. Tolga

TOLUNAY Assoc. Prof.

Dr. Fatih KARA

Spc. Dr. Bekir KESKİNKILIÇ

Publishing Commission

Publishing Commission of General Directorate of
Public Health

Editors

Dr. Murat TÜRKYILMAZ

Prof. Dr. Seçil ÖZKAN

Prof. Dr. Vahit ÖZMEN

Prof. Dr. M. Tezer KUTLUK

Prof. Dr. A. Serdar KARACA

Assoc. Prof. Nejat ÖZGÜL

Spc. Dr. Makbule ÖZTÜRK

Dr. Fahriye ÜNLÜ

Researcher İsmet DEDE

Sanitarian Selin DÜNDAR

Nrs. İlkay ATAĞ

PREFACE

It is inevitable that cancer will be a significant burden on the health system in the near future unless the essential interferences are not made, the measures are not taken as cancer is the second most common death cause in the world and in our country. Based on this fact, it is significantly crucial for our country to conduct cancer registration, epidemiological studies, cancer preventing and screening studies as part of our National Cancer Control Programme.

The most important step in preventing cancer development and cancer-related deaths is the implementation of an effective cancer registry system that allows analyzing current aspect, identifying the priorities and specifying proper strategies. Cancer registration ensures vital contributions to cancer control by several ways from identifying cancer burden and geographic range to understanding the causes for cancer, from population-based survival analyzes to evaluating the diagnosis, treatment and nursing quality of cancer. The number of our cancer registry centers whose data are included on the various versions of Cancer Incidence on Five Continents Book which is generally published in every five years by meeting the qualification criteria of the International Agency for Research on Cancer (IARC) in terms of the data quality are increasing day after day.

Our International Cancer Registry Center is one of the six regional training center of IARC and it provides training, consultancy and technical support to more than 30 countries.

As part of the cancer preventing actions, various researchs are carried out, programmes are developed and followed up pertinaciously in cooperation with relevant institutions and organizations. It is possible to decrease cancer by 1/3 rate, with the punctual effective interventions to preventable/modifiable risk factors (tobacco control, obesity control, physical activity, environmental effects, etc.) at the present time.

Screening standarts has been specified for breast, cervical (cervix), colorectal (large bowel) cancers, which are among the endemic cancers in the world and Turkey and they have been included in screening. Both early diagnosis and increasing lifetime and life quality are aimed with these screening programmes that are conducted successfully.

Our Phase III Cancer Control Programme has been prepared to evaluate the studies in our Phase I and Phase II Cancer Control Programmes that we prepared previously, to report their results and to ensure continuity of service.

Dr. Fahrettin KOCA

T.R. Ministry of Health

CONTRIBUTORS

Dr. Murat TÜRKYILMAZ	***Chairman of GDPH Cancer Department***
Prof. Dr. Fevzi ALTUNTAŞ	*Ankara Yıldırım Beyazıt University Faculty of Medicine Hematology Discipline*
Prof. Dr. Ali AYHAN	*Başkent University Faculty of Medicine Gynecologic Oncology Discipline*
Prof. Dr. Sancar BAYAR	*Ankara University Faculty of Medicine Dept. of General Surgery*
Prof. Dr. Seher DEMİRER	*Ankara University Faculty of Medicine Dept. of General Surgery*
Prof. Dr. Lütfi DOĞAN	*University of Health Sciences Faculty of Medicine Ankara AY Oncology Health Practices and Research Centre Surgical Oncology Clinic*
Prof. Dr. Mutlu DOĞAN	*University of Health Sciences, Dr. Abdurrahman Yurtaslan Ankara Oncology Health Practices and Research Centre, Medical Oncology Clinic*
Prof. Dr. Gonca ELCİN	*Hacettepe University Faculty of Medicine Dept. of USA*
Prof. Dr. Ganime DİLEK EMLİK	*Necmettin Erbakan University Meram Faculty of Medicine Dept. of Radiology*
Prof. Dr. Aslan GÜZEL	*Bahçeşehir University Gaziantep Medical Park Hospital, Neurosurgery Clinic*
Prof. Dr. A. Serdar KARACA	*Başkent University Faculty of Medicine Dept. of General Surgery*
Prof. Dr. Faruk KÖSE	*Acıbadem University Atakent Hospital Gynecologic Oncology Discipline*
Prof. Dr. M. Tezer KUTLUK	*Hacettepe University Faculty of Medicine and Cancer Institute Pediatric Oncology Discipline*
Prof. Dr. U. Fırat ORTAÇ	*Ankara University Faculty of Medicine Gynecologic Oncology Discipline*
Prof. Dr. Ö. Berna ÖKSÜZOĞLU	*Ankara University of Health Sciences Faculty of Medicine AY Oncology Health Practices and Research Centre Medical Oncology Clinic*
Prof. Dr. Seçil ÖZKAN	*Gazi University Faculty of Medicine Dept. of Public Health*
Prof. Dr. Vahit ÖZMEN	*Istanbul University Faculty of Medicine Dept. of General Surgery*

Prof. Dr. M. Coşkun SALMAN	*Hacettepe University Faculty of Medicine Gynecologic Oncology Discipline*
Prof. Dr. Zahide ŞİMŞEK	*University of Health Sciences Dışkapı Yıldırım Beyazıt Training And Research Hospital* *Gastroenterology Discipline*

Prof. Dr. Mustafa TUNAYA KALKAN	*Istanbul Aydın University Faculty of Medicine Dept. of Biophysics*
Prof. Dr. Gökhan TULUNAY	*TOBB University of Economics and Technology Gynecologic Oncology Discipline*
Prof. Dr. Ferah YILDIZ	*Hacettepe University Faculty of Medicine Dept. of Radiation Oncology*
Prof. Dr. Ülkü YILMAZ	*Atatürk Chest Diseases and Thoracic Surgery Training and Research Hospital Chest Diseases* *Clinic*
Prof. Dr. Kunter YÜCE	*Gynecologic Oncology*
Assoc. Prof. Dr. Hüseyin YÜCE BİRCAN	*Başkent University, Faculty of Medicine, Dept. of General Surgery*
Assoc. Prof. Dr. Murat GÜLTEKİN	*Hacettepe University Faculty of Medicine Gynecologic Oncology Discipline*
Assoc. Prof. Dr. Mehmet Enes GÖKLER	*Ankara Yıldırım Beyazıt University, Faculty of Medicine Dept. of Public Health*
Assoc. Prof. Dr. Nejat ÖZGÜL	*Hacettepe University Faculty of Medicine Gynecologic Oncology Discipline*
Dr. Faculty Member Hülya ŞİRİN	*University of Health Sciences Gülhane Faculty of Medicine Dept. of Public Health*
Dr. Faculty Member İnci YAMAN BAJİN	*Hacettepe University Faculty of Medicine and Cancer Institute Pediatric Oncology Discipline*
Spc. Dr. İrem BİLGETEKİN	*MOH. Dr. Abdurrahman Yurtaslan Training and Research Hospital*
Spc. Dr. Fatma BUĞDAYCI BAŞAL	*MOH. Dr. Abdurrahman Yurtaslan Training and Research Hospital*
Spc. Dr. İbrahim KARADAĞ	*MOH. Dr. Abdurrahman Yurtaslan Training and Research Hospital*
Surgeon Niyazi KARAMAN	*University of Health Sciences Faculty of Medicine Ankara AY Oncology Health Practices and Research Centre* *General Surgery Clinic*

Spc. Dr. Cengiz KARAÇİN	*MOH. Dr. Abdurrahman Yurtaslan Training and Research Hospital*
Spc. Dr. Serdar KARAKAYA	*MOH. Dr. Abdurrahman Yurtaslan Training and Research Hospital*
Spc. Dr. Ayşenur Beyazıt ÜÇGÜN	*Hacettepe University Faculty of Medicine Dept. of Public Health, Environmental Health Discipline*
Spc. Dr. Cansu ÖZTÜRK	*Keçiören Training and Research Hospital Radiology Clinic*
Help Desk Ufuk ÖZER	*Unit of Coordination of National Mammography Project*
Spc. Dr. Makbule ÖZTÜRK	*Head of Department of Cancer*
Dr. Fahriye ÜNLÜ	*Head of Department of Cancer*
Researcher İsmet DEDE	*Head of Department of Cancer*
Nrs. İlkay ATAĞ	*Head of Department of Cancer*
Nrs. Öznur KAYA	*Head of Department of Cancer*
Sanitarian . Selin DÜNDAR	*Head of Department of Cancer*
Nrs. Fatma KAYA	*Head of Department of Cancer*
Midwife Arzu SEVİNÇ	*Head of Department of Cancer*

CONTRIBUTING INSTITUTIONS AND ORGANIZATIONS

TR. MOH. GDPH Head of Department of Environmental Health
TR. MOH. GDPH Head of Department of Fight Against Tobacco and Substance Addiction
TR. MOH. GDPH Head of Department of Healthy Nutrition and Active Life

SYMBOLS AND ABBREVIATIONS

-A-

EU: European Union

Dept: Department of

ACS: American College of Surgeons

ACTH: Adreno Corticotropic Hormone

ADH: Atypic Ductal Hyperplasia

ADT: Androgen Deprivation Therapy

AFP: Alpha-Fetoprotein

FPIS: Family Practice Information

Systems AI: Aromatase Inhibitors

AJCC: The American Joint Committee on Cancer ALK: Anaplastic Lymphoma

Kinase

ALND: Axillary Lymph Node Dissection

ALL: Acute Lymphoblastic Leukemia

ALP: Alkalinephosphatase

AML: Acute Myelocytic Leukemia

APOCP: The Asian Pacific Organization for Cancer Prevention

ASCO: American Society of Clinical Oncology FHC: Family Health Center

ASTRO: American Society for Radiation Oncology

ATA: American Thyroid Association ATC: Anaplastic Thyroid Cancer

ATRT: Atypic Teratoid Rhabdoid Tumor

-B-

BCG: Bacillus Calmette-Guerin

LNI: Local Nodal Irradiation

CF: Cerebrospinal Fluid

CCT: Colonography with Computed Tomography

BSP: Bahçeşehir Screening Programme

CT: Computed Tomography

-C-

CAR: Chimeric Antigen Receptor CC: Craniocaudal

CONCORD Programme: Global surveillance of trends in cancer survival

CO_2: Carbon dioxide

CR: Computed Radiography

CT: Computed Tomography

-Ç-

DCBE: Duouble Contrast Baric Enama

-D-

LDCT: Low Dose Computed Tomography

DCIS: Ductal Carcinoma In Situ

DM: Digital Mammography

DM: Diabetes Mellitus

DMG: Digital Mammography

DMT: Digital Breast Tomosynthesis

DRE: Digital Rectal Examination

DTC: Differentiated Thyroid Cancers

-E-

EFVPTC: Encapsulated Follicular Variant of Papillary Thyroid Cancer

EBV: Ebstein Barr Virus

EMR: Endoscopic Mucosal Resection

ENCR: The European Network for Cancer Registries

EUROMED: Euro-Mediterranean Partnership (Cancer Network Project covering all European countries in the Europe-Mediterranean Region and countries in the Mediterranean Region)

EUS: Endoscopic Ultrasonography

EUSOBİ: Europian Society of Breast Imaging

EPIC: European Prospective Investigation into cancer and nutrition

ER: Endoscopic Resection

ERCP: Endoscopic Retrograde Choledocopancreatography

ESD: Endoscopic Submucosal Dissection

-F-

FAP: Familial Adenomatous Polyposis

FIGO: International Federation of Gynecology and Obstetrics

FISH: Fluorescence In Situ Hybridisation

IPIFL: International Prognostic Index for Follicular Lymphoma

FOB: Fiberoptic Bronchoscopy

FTC: Follicular Thyroid Carcinoma

-G-

GCO: Global Cancer Observatory FOB: Fecal Occult Blood

GIST: Gastrointestinal Stromal Tumours

-H-

HCV: Hepatitis C Virus

HHV: Human Herpes Virus

HL: Hodgkin Lymphoma

HLA: Human Leukocyte Antigen

HIP: Health Insurance Plan

HIV: Human Immun Deficiency Virus

HNPCC: Hereditary Non Polyposis Colorectal Cancer

HPV: Human Papilloma Virus

HR: Hormone Receptor

HRT: Hormone Replacement Therapy

PHIS: Public Health Information System

GDPH: General Directorate of Public Health

PHMS: Public Health Management System

HUB: Centre ("International Cancer Registration Regional Centers" mentioned in the text)

HTLV-1: Human T Lymphocyte Virus-1

-I-

IACR: The International Association of Cancer Registries

IARC: The International Agency for Research on Cancer

IASLC: The International Association for the Study of Lung Cancer

ICNIRP: The International Commission on Non-Ionizing Radiation Protection

IEC: The International Electrotechnical Commission

INHANCE: International Head and Neck Cancer Epidemiology

IMDC: The International Metastatic Renal Cell Carcinoma Database Consortium

IPI: International Prognostic Index

IPRI: The International Prevention Research Institute

ITU: The International Telecommunication Union

-I-

IDK: Invasive Ductal Carcinoma

ICIT: Immune Checkpoint Inhibitor Therapy

ILC: Invasive Lobular Carcinoma

IMK: Invasive Mixed Carcinoma

FNAB: Fine-needle Aspiration Biopsy

-J-

JME: Japan Molecular Epidemiology

JMML: Juvenile Myelomonocytic Leukemia

-K-

KazIOR: Kazakhistan Institute of Oncology and Radiology

HDC: Head of Department of Cancer

SCLC: Small Cell Lung Cancer

NSCLC: Non-Small Cell Lung Cancer

CESTC: Cancer Early Diagnosis, Screening and Training

Center DL: Decree Law

CNB: Core-Needle Biopsy

TRNC: Turkish Republic of Northern Cyprus

CML: Chronic Myelogenous Leukemia

CRC: Colorectal Cancer

C-RT: Chemo-Radiotherapy

CAS: Cancer Appointment System

CRPC: Castration-Resistant Prostate Cancer

CSM: Contrast-enhanced Spectral Mammography

CEDC: Cancer Early Diagnosis Center

BSE: Breast Self-Examination

-L-

LAP: Lymphadenopathy

LBC: Liquid Based Cytology

LABC: Locally Advanced Breast Cancer

-M-

MECC: The Middle East Cancer Consortium

MEC: Mucoepidermoid Carcinoma

MEN: Multiple Endocrine Neoplasia

MEMEDER: Breast Health Association

MG: Mammography

MI: Mammaria Interna

MIPI: Mantle cell lymphoma international prognostic index

MLO: Mediolateral Oblique

MNG: Multinodular goiter

MR: Magnetic Resonance

MRD: Minimal Residual Disease

MRCP: Magnetic resonance cholangiopancreatography

MRS: Magnetic Resonance Screening

MRM: Modified Radical Mastectomy

MKC: Breast Sparing Surgery

MÜSİAD**:** Independent Industrialists and Businessmen's Association

MZL: Marginal Zone Lymphoma

-N-

NCCN: National Comprehensive Cancer Network

NCI: The National Cancer Institute

NHL: Non-Hodgkin Lymphoma

NHS**:** The National Health Service

NIFT-P: Noninvasive Follicular Thyroid Neoplasm

NIH: National Institute of Health

NLST: National Lung Cancer Screening Trial

NMZL: Nodal Marginal Zone Lymphoma

NSCLC: Non-Small-Cell Lung Cancer

-O-

OECD: Organisation for Economic Co-operation and Development

OPS: Oncoplastic Surgery

-O-

ER: Estrogen receptor

-P-

PACT: Programme of Action for Cancer Therapy

PBDE: Polybrominated Diphenyl Ether

PCR: Polymerase Chain Reaction

PDGFRA: Platelet-derived growth factor receptor alpha

PET: Positron Emission Tomography

PBR: Partial Breast Radiotherapy

Pthrp: Parathyroid hormone related protein

PTK: Papillary Thyroid Cancer

PTL: Primary Thyroid Lymphoma

Ptx: Prophylactic

Thyroidectomy

-R-

RAIT: Radioactive Iodine Therapy

ROLL: Roll Biopsy

RT: Radiotherapy

-S-

SCCHN: Squamous Cell Carcinoma of the Head and Neck

HLC: Healthy Life Centre

SEER: The Surveillance, Epidemiology, and End-Results

SEEHN: South-Eastern Europe Health Network

SERM: Selective Estrogen Receptor Modulator SSI: Social Security Institution

SLL: Small Lymphocytic Lymphoma

SLN: Sentinel Lymph Node

SLNB: Sentinel Lymph Node Biopsy

CLND: Central Lymph Node Dissection

SPECT: Single-Photon Emission Computed Tomography

SMTC: Sporadic Medullary Thyroid Carcinoma

SRS: Stereotactic Radiosurgery

SRT: Stereotactic Radiotherapy

SSO: Society of Surgical Oncology CNS: Central Nervous System

CHP: Communiqué on Healthcare Practices

-T-

TAIEX: The Technical Assistance and Information Exchange ınstrument

TEMLA: Transcervical Extended Mediastinal Lympadenectomy

TFNAB: Transbronchial Fine-needle Aspiration Biopsy

TCGA: The Cancer Genome Atlas

TFT: Thyroid Function Tests

TKI: Tyrosine Kinase Inhibitor

TOBB-ETU: The Union of Chambers and Commodity Exchanges of Turkey University of Economics and Technology

TFBDA: Turkey Federation of Breast Diseases Association

RWB: Radiotherapy of the Whole Breast

TNM: Tumor Node Metastasis

TSPH: Turkish Society Of Pediatric Hematology

TPO: Thyroid Peroxidase

TPOG: Turkish Pediatric Oncology Group

TSR: Turkish Society of Radiology

TRUS: Transrectal Ultrasonography

CHC: Community Health Center

TRT: Transurethral Resection of Tumor

TURNOG: Turkish Neurosurgical Society Neurooncology Group

TSI: Turkish Statistical Institute

Ttx: Total Thyroidectomy

-U-

UICC: The Union for International Cancer Control

NCCP: National Cancer Control Programme

NBCD: National Breast Cancer Database

US: Ultrasonography

-W-

WHO: The World Health Organization

-V-

VAMLA: Video-Assisted Mediastinal Lymphadenectomy

VATS: Video-Assisted Thoracoscopic Surgery

VAB: Vacuum Assisted Biopsy

VEGF: Vascular Endothelial Growth Factor

BMI: Body Mass Index

VMA: Vanillylmandelic Acid

-Y-

ASR: Age Standardized Rates

TABLES

Introduction: Why a National Cancer Control Programme

Table 1. Distribution of Top Five Cancer Types Which Are Most Common in Males According to Data of Globocan 2020 Published by International Agency for Research on Cancer (IARC)

Table 2. Distribution of Top Five Cancer Types Which Are Most Common in Females According to Data of Globocan 2020 Published by International Agency for Research on Cancer (IARC)

Section 1: Cancer Registration

Table 1. Status of Turkey According to Data of Globocan 2020 published by International Agency for Research on Cancer (IARC) (Age Standardized Rates/ per 100.000 individuals)

Table 2. Cancer Registry Centers and Reference Dates in Turkey

Table 3. Distribution of Years That Active Cancer Registry Centers Were Reported in Turkey

Section 2: The Most Common Adulthood and Childhood Cancer Types in Turkey

Table 1. Histopathologic Subtypes of Lung Carcinoma According to 2015 Classification of World Health Organisation

Table 2. Percentage Distribution of Histological Subtypes of Thorax Cancers

Table 3. "T" Definitions According to Eighth Edition of Tumor, Node, and Metastases Staging System

Table 4. Lung Cancer Eighth TNM Staging System

Table 5. Presenting Symptoms of 18.363 Gastric Cancer Patients

Table 6. Staging according to FIGO (International Federation of Gynecology and Obstetrics) System in Endometrial Carcinoma

Table 7. Histopathologic Types of Uterine Cancer According to Classification of World

Health Organisation

Table 8. WHO Classification of Mature Lymphoid Neoplasias 2016

Table 9. WHO Classification of Lymphoblastic Leukemia/Lymphoma 2016

Table 10. Classification of NHL According to Traits of Clinical

Course

Table 11. Typical Immunophenotypic Traits in Common B Cell NHL

Table 12. Revise Staging System for Primary Nodal Lymphomas (Lugano Classification)

Table 13. Lugano Criterion for Lymphoma Response Assessment

Table 14. Survival Time According to IPI Scores for Aggressive NHL

Table 15. Survival Time According to Age-adjusted IPI (aaIPI) Scores for Aggressive NHL

Table 16. NCNN- IPI Scoring

Table 17. Survival Time According to NCNN-IPI Scores

Table 18. International Prognostic Index for Follicular Lymphoma (IPIFL)

Table 19. Mantle Cell Lymphoma International Prognostic Index (MIPI)

Table 20. Survival Time According to MIPI Scores

Table 21. Survival Time Acccording to PIT Scores

Table 22. FIGO Stage in Epithelial Overian-Tube-Peritoneal Cancers (2013)

Table 23. Age-Standardized Cancer Incidences and Number of Cases in Children in the World, IARC, 2018

Table 24. Turkish Pediatric Oncology Group and Turkish Society of Pediatric Hematology Distribution of Children's Cancer 2009-2019

Table 25. Effects of Chromosomal Abnormalities in ALL on Prognosis

Table 26. WHO Classification of Acute Myelocytic Neoplasms

Table 27. Effects of Common Chromosomal Abnormalities in AML on Prognosis

Section 3: Primary Protection

Table 1. Causes and Rates of Carcinogenicity

Table 2. Diet, Nutrition and Cancer: Levels of Evidence

Table 3. Frequency of Alcohol Use According to Years in the Population Aged 15 and Older in Turkey

Table 4. Carcinogenicity Classification defined by International Agency for Research on Cancer

Section 4: Secondary Protection

Table 1. World Samples of Colorectal Cancer Screening Programmes

Table 2. BI-RADS Outcome Assessment Categories

Table 3. Breast Morphologies in Mammography

Table 4. Meanings of Suspicious Symptoms Reported on Mammography

Table 5. Screening Mammography Reporting Unit

Section 5: Tertiary Protection

Table 1. TNM Definitions

Table 2. Clinical Anatomical Staging

Table 3. Clinical Prognostic Staging System

Table 4. Endocrine Treatment Options in Hormone Receptor Positive Metastatic Disease

Section 7: Cancer Burden in the World and Turkey

Table 1. Causes of Death in 2017 Turkish Statistical Institute (TSI)

Table 2. Distribution of Cancer According to Continents, IARC 2018

Table 3. Cancer Incidences and Deaths in 2018 in the World IARC, 2018

Table 4. The Most Common 10 Cancer Types in Both Gender in the World, IARC, 2018

Table 5. The Most Fatal 10 Cancer Types in Both Gender in the World, IARC, 2018

Table 6. The Most Common 10 Cancer Types in Males in the World, IARC, 2018

Table 7. The Most Fatal 10 Cancer Types in Males in the World, IARC, 2018

Table 8. The Most Common 10 Cancer Types in Females in the World, IARC, 2018

Table 9. The Most Fatal 10 Cancer Types in Females in the World, IARC, 2018

Table 10. The Most Common 10 Cancer Types in Both Gender in Turkey, GLOBOCAN, 2018

Table11. The Most Fatal 10 Cancer Types in Both Gender in Turkey, GLOBOCAN, 2018

Table 12. The Most Common 10 Cancer Types in Males in Turkey, GLOBOCAN, 2018

Table 13. The Most Fatal 10 Cancer Types in Males in Turkey, GLOBOCAN, 2018

Table 14. The Most Common 10 Cancer Types in Females in Turkey, GLOBOCAN, 2018

Table 15. The Most Fatal 10 Cancer Types in Females in Turkey, GLOBOCAN, 2018

FIGURES

Introduction: Why a National Cancer Control Programme

Figure 1. Distribution of Age Standardized Incidence Rates for All Cancers According to Gender Between 2008 and 2017 (Turkey Compositional Data Base, 2008-2017) (World Standard Population, per 100,000 individuals)

Figure 2. Projection of Cancer Incidence for Turkey between 2017-2023

Figure 3. Age-Standardized Rates of 10 Cancer Types Which Are Most Common in Males (Turkey Compositional database, 2017) (World Standard Population, per 100,000 individuals)

Figure 4. Age-Standardized Rates of 10 Cancer Types Which Are Most Common in Females (Turkey Compositional database, 2017) (World Standard Population, per 100,000 individuals)

Figure 5. Age-Standardized Rates and Percentages of Tobacco Use for All Cancers and Lung Cancer in Some Countries, GLOBOCAN 2020

Figure 6. SEER Summary Staging Distribution of Screening Cancers (Turkey Compositional Data Base, 2017)

Figure 7. WHO Strategies for National Cancer Control Programme: Establishing Standards

Figure 8. National Cancer Control Programme

Section 1: Cancer Registration

Figure 1.1. Age-Standardized Rates of 5 Most Common Cancer Types in Males by Region, in the World, per 100,000 individuals (GLOBOCAN 2020)

Figure 1.2. Age-Standardized Rates of 5 Most Common Cancer Types in Females On the Basis of Region, in the World, per 100,000 individuals (GLOBOCAN 2020)

Section 2: The Most Common Adulthood and Childhood Cancer Types in Turkey

Figure 1. Age-Standardized Rates of 10 Cancer Types Which Are Most Common in Males (Turkey Compositional database, 2017) (World Standard Population, per 100,000 individuals)

Figure 2. Age-Standardized Rates of 10 Cancer Types Which Are Most Common in Females (Turkey Compositional database, 2017) (World Standard Population, per 100,000 individuals)

Figure 3. Percentage Distribution of Lung Cancer Stages (Turkey Compositional Data Base, 2017)

Figure 4. Assessment of Zonal Lymphatic Gland on Non-Metastatic NSCLC

Figure 5. Primary Brain Cancer (Glioblastoma Multiforme)

Figure 6. Metastatic (Lung-derived) Brain Cancer

Figure 7. Percentage Distribution of Cancers in Children Aged 0-14 Group Within This Group (Turkey Compositional Data Base, 2016)(Other/Except for Unspecified Malignant Neoplasms)

Section 3: Primary Protection

Figure 1. Number of Case of Newly Diagnosed Cancer Types in Males and Females Worldwide in 2018 (All Age Groups)

Figure 2. Process of Cancer Development in Tobacco Use

Figure 3. Health Improvement Model in Cancer Screening: What, Who, How

Figure 4. The Effectiveness of Intervention Strategies in Cancer Screening

Section 4: Secondary Protection

Figure 1. Chart of Disease Stages and Screening Time

Figure 2. Screening Methods in Breast Cancer

Figure 3. Screening of High Risk Group for Breast Cancer

Figure 4. Distribution of Final Diagnoses of Cases with BIRADS 5 as a Screening

Result

Figure 5. Distribution of Final Diagnoses of Cases with BIRADS 4 as a Screening

Result

Figure 6. Cases with BIRADS 0 as a Screening Result

Figure 7. Cervical Cancer Incidence in the World (GLOBOCAN 2018)

Figure 8. Age-Standardized Rates of 10 Cancer Types Which Are Most Common in Females (Turkey Compositional database, 2017) (World Standard Population, per 100,000 individuals)

Figure 9. New Algorithm of Turkey Cervical Screening Programme, 2020

Figure 10. WHO Cervical Cancer Elimination Programme 2030 Targets

Figure 11.WHO Cervical Cancer Elimination Programme 2030, 2090, 2120 Targets

Figure 12. Colorectal Cancer Incidence in the World (GLOBOCAN 2018)

Figure.13. Breast Zones Aks: Armpit M: Central Section of Breast

Figure 14. Screening Mammography Report Example

Figure 15. Detailed Algorithm of National Screening Mammography Reporting

Section 5: Tertiary Protection

Figure 1. Simulation with Computed Tomography (CT) in a Patient Planned for Radiotherapy

Figure 2. Drawing of Target Volume and Surrounding Normal Tissues and Organs on Computed Tomography (CT) Sections

Figure 3. Treatment Planning and Dose Volume Histogram

Figure 4. Breast Areas Aks: Armpit M: Central Section of Breast

Section 7: Cancer Burden in the World and Turkey

Figure 1. Causes of Death in the World, 2011 (World Cancer Report, 2014)

Figure 2. Number of Cases in Both Gender in 2018 in the World, 2018, IARC

Figure 3. Cancer Deaths in Both Gender in 2018 in the World, 2018, IARC

Figure 4. Number of Cases in Males in 2018 in the World, 2018, IARC

Figure 5. Cancer Deaths in Males in 2018 in the World, 2018, IARC

Figure 6. Number of Cases in Females in 2018 in the World, 2018, IARC

Figure 7. Cancer Deaths in Females in 2018 in the World, 2018, IARC

Figure 8. Number of Cases in Both Gender in 2018 in Turkey, 2018, IARC

Figure 9. Cancer Deaths in Both Gender in 2018 in Turkey, 2018, IARC

Figure 10. Number of Cases in Males in 2018 in Turkey, 2018, IARC

Figure 11. Cancer Deaths in Males in 2018 in Turkey, 2018, IARC

Figure 12. Number of Cases in Females in 2018 in Turkey, 2018, IARC

Figure 13. Cancer Deaths in Females in 2018 in Turkey, 2018, IARC

Figure 14. Distribution of Age Standardized Incidence Rates for All Cancers According to Gender Between 2013 and 2017 (Turkey Compositional Data Base, 2013-2017) (World Standard Population, per 100,000 individuals)

Figure 15. Age-Standardized Rates of 10 Cancer Types Which Are Most Common in Males (Turkey Compositional database, 2017) (World Standard Population, per 100,000 individuals)

Figure 16. Age-Standardized Rates of 10 Cancer Types Which Are Most Common in Females (Turkey Compositional database, 2017) (World Standard Population, per 100,000 individuals)

Figure 17. Percentage Distribution of Some Most Common Cancers in Males of All Age Groups Within This Group (Turkey Compositional Data Base, 2017)

Figure 18. Percentage Distribution of Some Most Common Cancers in Females of All Age Groups within This Group (Turkey Compositional Data Base, 2017)

TABLE OF CONTENT

HISTORICAL DEVELOPMENT 1-6

INTRODUCTION 7

Why a National Cancer Control Programme.....7-14

Developmental Stages of Turkey National Cancer Control Programme... 15-17

Principles of a National Cancer Control Program 17-19

SECTION 1: CANCER REGISTRATION…..... 21-24

1.1. Cancer Registry System in Turkey.....25-30

1.2. Active Cancer Registry Activities Conducted in Turkey 30-31

1.2.1 Data Gathered by Active Cancer Registry System.....31-32

1.2.2 Data Sources in Active Cancer Registry System 32-33

Quality Control in Active Cancer Registry System 33-34

1.3. Reliability in Cancer Registry System and Quality Control Evaluations.....34-37

SECTION 2: THE MOST COMMON ADULT AND CHILDHOOD CANCER TYPES IN TURKEY… 39

2.1. Trachea, Bronchial, Lung Cancer… 40-75

2.2. Breast Cancer (Book Chapter) 76

2.3. Prostate Cancer… 76-84

2.4. Colorectal Cancer (Book Chapter) 85

2.5. Thyroid Cancer… 85-106

2.6. Bladder Cancer… 106-111

2.7. Gastric Cancer… 111-122

2.8. Uterus Corpus... 122-131

2.9. Kidney Cancer… 132-138

2.10. Non-Hodgkin Lymphoma... 138-162

2.11. Ovary Cancers 162-170

2.12. Laryngeal Cancer..... 171-179

2.13. Pancreatic Cancer... 179-191

2.14. Brain and Nervous System Cancers 191-200

2.15. Skin Cancer 200-212

2.16. Childhood Cancer Types 212-249

3. SECTION: PRIMARY PROTECTION.....251

3.1. GENERAL INFORMATION 252

3.2. ETIOLOGIC RISK FACTORS OF CANCER 253

3.2.1. Tobacco Use... 253

3.2.2. Nutrition and Obesity… 253

3.2.3. Alcohol USe 253

3.2.4. Infectious Factors… 253-254

3.2.5. Vocational Risks and Air Pollution… 254

3.2.6. Ionizing and Non-ionizing Radiation… 254

3.2.7. Global Cancer Burden... 254-255

3.2.8. Primary and Secondary Protections..... 255-258

3.3. COUNTRY SAMPLES IN CANCER SCREENING… 258-261

3.4. PROTECTION STRATEGIES… 262

3.4.1. Primary Protection... 262-291

3.5. AWARENESS RAISING ACTIVITIES IN THE WORLD AND IN TURKEY 291-299

SECTION 4: SECONDARY PROTECTION..... 301

4.1. Cancer Screenings… 302

4.1.1. What is Screening? Why is Cancer Screening Done? 302-306

4.1.2. Breast Cancer Screenings… 306-333

Annexing 1-(07.11.2021)-4.1.3.What is National Screening Mammography?. 333

4.1.3.1. How to Do Reporting in National Screening Mammography**?.....**333-336

4.1.3.2. How Does the Reporting Algorithm Function? 336

4.1.3.3. How Do Report Results Seem? 336-339

4.1.4. Head of Department of Cancer Central Reading Report Result 340-341

4.1.5. Cervical Cancer Screening 342-361

4.1.6. Colorectal Cancer Screening.....362-376

SECTION 5: TERTIARY PROTECTION..... 377

5.1. Post Screening Diagnosis and Treatment Centers 378-381

5.2. Diagnosis, Clinical Stating and Treatment Methods in Breast Cancer Which is One of The Most Common Cancers..... 381

5.2.1. Diagnosis in Breast Cancer… 381

5.2.1.1 Anamnesis and Physical Examination.....381-385

5.2.1.2. Diagnostic Radiological Methods in Breast Cancer.....385-388

5.2.1.3. Biopsy Methods in Breast Cancer 388-393

5.2.2. Clinical Staging in Breast Cancer 394-400

5.2.2.1 Multidisciplinary Approach After Staging… 400-402

5.2.3. Treatment in Breast Cancer… 403

5.2.3.1. Surgical Treatment in Breast Cancer 403-420

5.2.3.2. Systemic Treatment in Breast Cancer 420-428

5.2.3.3 Radiotherapy in Breast Cancer Treatment 428-437

SECTION 6: INTERNATIONAL ORGANIZATIONS AND ACTIVITIES… 439

6.1. WHO: World Health Organization... 440

6.2. International Agency for Research on Cancer (IARC) 441-442

6.2.1. IARC-Western Asia, Central Asia and Northern Africa Regional Center for Cancer Registry ARC-İZMİR HUB 442-443

6.3.European Union Scientific Commission... 443-444

6.4.UICC: Union for International Cancer Control… 444-445

6.5.Meetings of the US Cancer Institute and World Cancer Leaders… 445-446

6.6.IPRI: The International Prevention Research Institute.....446

6.7.APOCP: The Asian Pacific Organization for Cancer Prevention 446

6.8.EUROMED 447

6.9.SEEHN: South-Eastern Europe Health Network… 447-448

6.10.Albanian Embassy - MÜSİAD.....448

SECTION 7: CANCER BURDEN in THE WORLD AND in TURKEY 449-470

SECTION 8: CANCER ACTION PLANS 471-476

HISTORICAL DEVELOPMENT

1947: The first regulations on cancer were made in conjunction with Turkish Association for Cancer Research and Control.

1955: The construction of Ankara Ahmet Andiçen Oncology Hospital started.

1962:

- Ankara Ahmet Andiçen Hospital was assigned to Ministry of Health to be run.
- Cancer, which was counted among other diseases until 1962, was started to be considered seperately after the **establishment of Cancer Branch Chieftainship** beneath Basic Health Services.

1967: Etimesgut Oncology Hospital was established by the Ministry.

1970:

- **Department of Cancer Control** was established within Basic Health Services.
- Week of April 1-7 was recognized as Week of Cancer

1972-1976: In-service trainings and public education were organized by Ministry on cancer screening in our country.

1977: Cancer Control Council was established.

1982: Cancer was included in **mandatory reporting** diseases (Article 57 of Public Health Law in Turkey No 1593).

1983:

- Cancer registry was started through a passive system in our country once cancer was included in the group of mandatory reporting diseases.

- Head of Department of Cancer Control was established within Ministry of Health by DL No 181 (Official Gazette (OG) no 18251 and dated 12.14.1983)
- Science Committee of Cancer Control was established (May 14, 1983).
- Oncology was recognized as sub-branch.

1989:

- Turkey became a member of The Union for International Cancer Control (UICC).
- The number of Medical Oncologists reached to 8, Pediatric Oncologists reached 7 and the number of Surgical Oncologists reached 4.

1992: Cancer Registry and Incidence Project was primarily launched in İzmir.

1995: The studies of Cancer Screening Project was started, the first Cancer Early Diagnosis Center (CEDC) was established in Bakırköy Public Hospital.

1996: Tülay Aktaş Cancer Early Diagnosis Centers were put into service in Ankara Ahmet Andiçen Additional Service Building (April 1, 1996) and in Narlıdere, İzmir.

1997: Awareness studies were conducted for the first time on asbestos

1998:

- Training for physician and other healthcare personnels of CEDC was organized for the first time in Ankara Oncology Hospital.
- Antalya province Cancer Registry Center was incorporated into Active Cancer Registry as second province.

2000:

- **Cancer Early Diagnosis Center Regulation** (12.14.2000- OG No 24260) was published.
- **Cancer Registry Centers Regulation** (12.14.2000- OG No 24260) was published.

2001:

- Training of "Breast Self-Examination" was started in cities.
- International Cancer Consultative Committee, Mesothelioma, and Inherited Cancer Commitee were established.
- The Asian Pacific Organization for Cancer Prevention was organized in İzmir, the first Head of Department and CESTC's poster were also presented.

2003: The membership of our country was accepted at The Middle East Cancer Consortium (MECC) held in Geneve.

2004

- Cancer Early Diagnosis, Screening and Training Centers (CESTC) conforming to standards of EU were put into action with EU donation funds in 11 provinces. CEDCs in 31 provinces were integrated into CESTC.
- National Standards Circular No 2004/99 for Breast Cancer Screening in Women was published (dated 07.20.2004 and issue 1135)

2005: International Cancer Consultative Committee and sub-committees were established through directive.

2006

- Training Skills Course for CESTC personnels was organized and was carried out theoretically and practically for 26 times in 5 years.
- Research of Black Sea Cancer and Cancer Risk Factors is conducted due to Chernobyl Nuclear Power Plant accident.

2007

- Kocaeli Active Cancer Registry Center was established.
- The data of Izmir and Antalya Cancer Registry Centers (1998-2002 series) were included in the Ninth Edition of Cancer Incidence on Five Continents Book published by International Agency for Research on Cancer (IARC)

- Standards of National Cancer Screening on the Breast, Cervical and Colorectal Cancers were published.

2009:

- 34 Woman and Family Health Center of Istanbul Metropolitan Municipality went into action by protocol as CESTC in addition to 88 CESTC in 81 provinces on July 14, 2009.
- National Cancer Control Programme was published (Phase I:2009-2015)
- Meetings of palliative care centers were held with WHO.

2010: Gaziantep and Malatya provinces were added to Active Cancer Registry Centers.

2011:

- Head of Department of Cancer affiliated to Public Health Agency of Turkey was restructured by DL No 663 (11.02.2011)
- Head of Department of Cancer (HDC) has become a member of International Agency for Research on Cancer (IARC)

2012:

- The number of Active Cancer Registry Centers increased to 13 after Mersin and Istanbul provinces were added.
- CESTCs were reidentifed as Units Affiliated to Community Health Centers after their restructuring by Ministry with DL No 663 (03.19.2012)
- Studies of "Turkey Asbestos Control Strategic Plan" were initiated with the participation of academicians and were generalized throughout the country. The assessment of the current circumstance throughout the country is called Phase I, and the necessary improvement works are called Phase II in the program.

2013:

- Active Cancer Registry was started in all 81 provinces.

- The data from Izmir, Antalya, Trabzon, Edirne, Bursa, Erzurum, Eskişehir ve Samsun Cancer Registry Centers (2008-2012 series)

  10. were included in the "Cancer Incidence on Five Continents Book" published by IARC.
- Izmir Cancer Registry Center has become a cancer registry training center (HUB) for countries located in Northern Africa and the Eastern Mediterranean region by IARC because of its 20 years of experience and continuity.
- Family physicians were integrated into cancer screening programs by Familiy Practice Implementing Regulation.
- It was planned to form "Turkey Radon Map" by measurements in 81 provinces and then to improve "National Radon Control Programme". Our General Directorate and the Turkish Atomic Energy Authority signed a cooperation protocol on 03.15.2013 to jointly conduct the project within this scope.
- Mobile cancer screening vehicle which belongs to the partnership of TOBB-ETU Hospital and KESTELLI was granted to Ministry to do screening in provinces.
- Standards of National Cancer Screening on the Breast, Cervical and Colorectal Cancers was published after being revised.

2014:

- FPIS programme used by family physicians was integrated into HYBS.
- Data base of PHIS went into action in such a manner that primary healthcare providers will use.
- The community-based cervical cancer screening program conducted with the Pap-smear test was renovated and the HPV-DNA test was added.
- Reference laboratories were established in Ankara and Istanbul to evaluate HPV-DNA tests.
- The community-based cervical cancer screening program was generalized throughout 81 province.
- The meeting of International Cancer Consultative Committee and sub-committees was held and cancer reports were regulated.

2015: **Cancer Register Centers Regulations** (06.03.2015- O.G. numbered 29375 was published.

2016:

- Mobil Mammography Pilot Implementation and Central Reporting Project were launched to increase the effectiveness of community-based breast cancer screening programme conducted with mammography in primary healthcare.
- National Cancer Control Programme was published (Phase II:2016-2018)

2017:

- General Directorate of Public Health was established.
- Head of Department of Cancer was established with Directive dated 10.02.2017 and numbered 04.495 on GDPH Service Units and Duties.
- The data from Izmir, Antalya, Trabzon, Edirne, Bursa, Erzurum, Eskişehir ve Samsun Cancer Registry Centers (2008-2012 series)

  11. were included in the edition of The "Cancer Incidence on Five Continents Book" published by IARC.
- PHMS data base went into action.

2018

- Data and survivals of 18 cancer types from 322 population-based cancer registry centers in 71 countries were published in Global Surveillance of Trends in Cancer Survival 2000–14 (CONCORD-3). Data of nine cancer registry centers in our country were included among these centers (Ankara, Antalya, Bursa, Edirne, Erzurum, Eskişehir, İzmir, Samsun ve Trabzon Cancer Registry Centers.)
- Studies of Diagnosis Centers Module were initiated to keep records regularly after screening.

2019:

- Cancer Registration Circular (dated 04.16.2019 and numbered 23776858-157.99.242) was sent to the provinces.
- Public Health Management System Cancer Appointment System (CAS) software studies of Call Center initiated for Cancer Screenings by Directorate General for Health Information Systems were completed and pilot scheme was started in three provinces.

INTRODUCTION

Why a National Cancer Control Programme

Like all over the world, cancer is one of the most important public health problems in Turkey. Cancer is the second cause of death both in the world and in Turkey. Nearly one in every 6 deaths worldwide and one in every 5 deaths in our country are because of cancer [1,2]. While It was estimated that 18 million people got cancer in 2018, it is predicted that this number will have increased to 30 million by 2040 [3].

Approximately one third of cancer deaths result from five primary risk factors related to behaviour and nutrition: Tobacco use, high body mass index (being overweight or obese), poor nutrition in fruits and vegetables, insufficient physical activity and alcohol use. Tobacco use is the most important risk factor to cancer and is responsible for 22% of cancer deaths [1].

The increase in cancer indicences that will be observed as a result of world population growth, aging and being more exposed to etiological factors will also lead to an increased cancer burden [4,5].

This rapid increase of cancer burden constitutes a significant crises for public health and health systems worldwide. In the future, it will be an important problem to ensure adequate allowance for the treatment of a vast number of cancer patients to be diagnosed and their palliative, supportive and death phase care for several countries including countries with abundant resources [3].

In fact, all countries, regardless of resource levels, have a chance of success in cancer prevention [4]. Almost 30-50% of cancers at the present time are preventable by avoiding risk factors and implementing the available evidence-based preventing strategies . In addition, several cancer patients who were diagnosed early and treated in an appropriate way are also likely to recover [1].

The change in the cancer incidence frequency by years in our country is presented in Figure 1. Looking at the cancer statistics of 2008-2017, it is seen that the cancer incidences in both genders follow a similar trend in the distribution between the years.

When the data of 2017 is evaluated; it is seen that approximately 180,288 new cancer cases emerged in our country within a year.

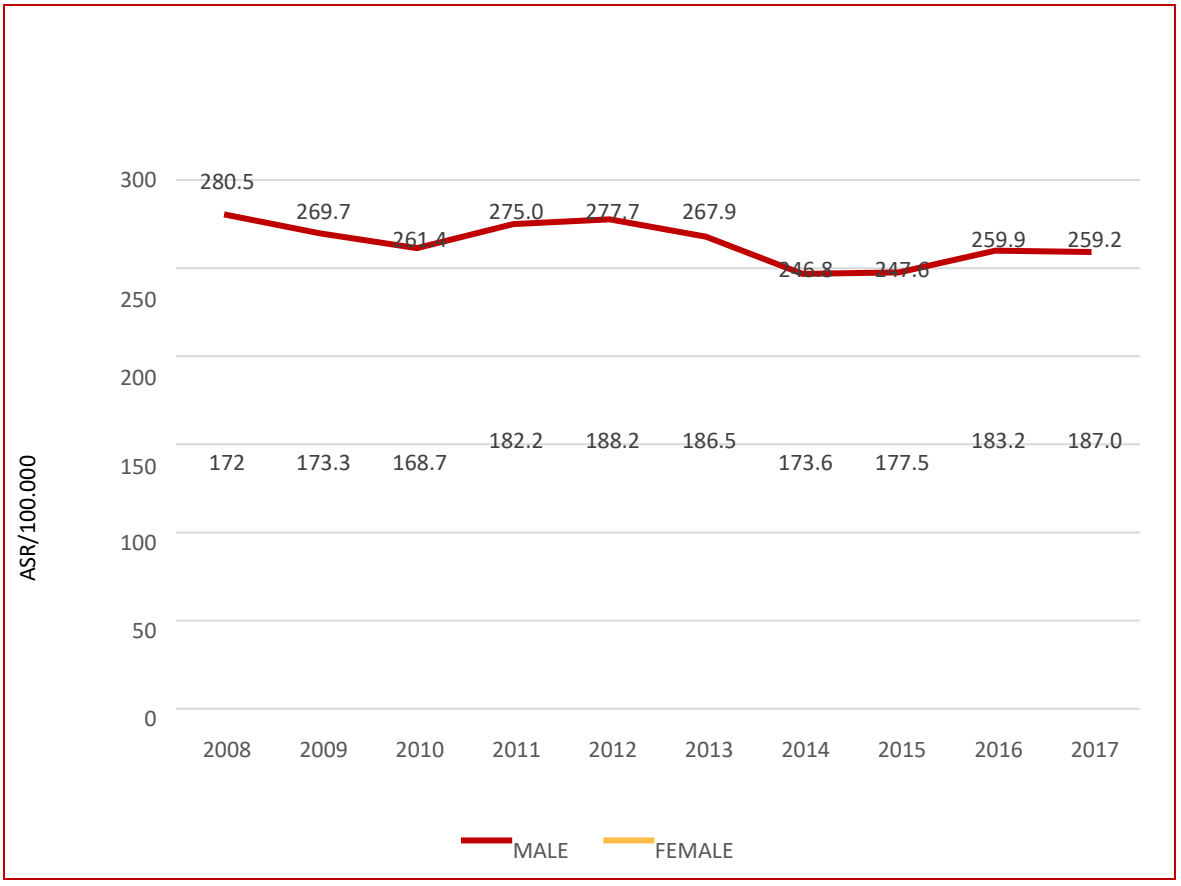


Figure 1. Distribution of Age Standardized Incidence Rates for All Cancers According to Gender Between 2008 and 2017 (Turkey Compositional Data Base, 2008-2017) (World Standard Population, per 100,000 individuals)

Considering the projection of cancer incidence in our country between 2017 and 2023, it is estimated that there will be an increase within years (Figure 2).

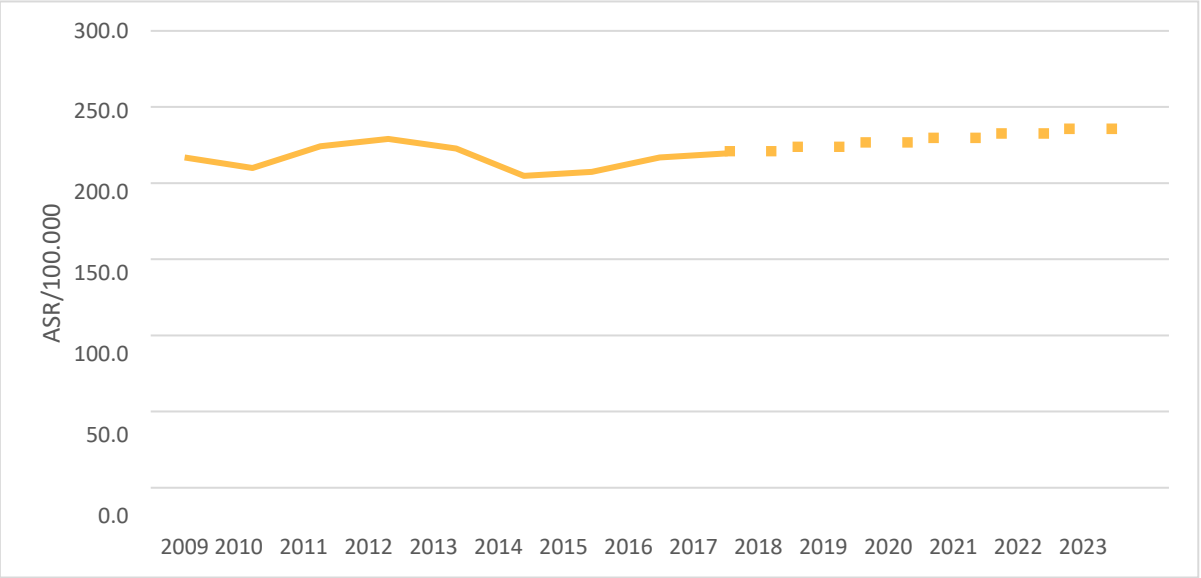


Figure 2. Projection of Cancer Incidence for Turkey between 2017-2023

(Resource: T.R. Ministry of Health GDPH Head of Department of Cancer)

Turkey is one of the countries where geographical, cultural, economic and social differences can be observed. These differences leads to a much more complicated situation in the case of controlling a disease like cancer that can develop in relation to a large number of factors. Since cancer is not a disease that can only be explained with genetic susceptibility. It is a type of disease that can develop due to primarily smoking, nutrition, inhaled air, environmental conditions, sedentary lifestyle, technological developments and many other factors.

The first 5 cancer types observed in our country show similarities with the pattern in the world and other developed countries (Table 1,2) [3,6]. Trachea, bronchial and lung cancers are the most common cancer types in males (56.7/per 100.000 individuals ASR) and breast cancer is the most common cancer type in females (47.7/ per 100.000 individuals ASR). Colorectal cancers rank third place in both males and females and it is observed in males at a frequency of 25.1 per hundred thousand and in females at a frequency of 14.7 per hundred thousand (Figure 3,4).

Table 1. Distribution of Top Five Cancer Types Which Are Most Common in Males According to Data of Globocan 2020 Published by International Agency for Research on Cancer (IARC)

	Turkey*	**World**	**Western Asia**	**Central and Eastern Europe**	**USA**
1	Lung	Lung	Lung	Lung	Prostate
2	Prostate	Prostate	Prostate	Prostate	Lung
3	Colorectal	Colorectal	Colorectal	Colorectal	Colorectal
4	Bladder	Stomach	Bladder	Stomach	Bladder
5	Stomach	Liver	Stomach	Bladder	Skin Melanoma

* Turkey Compositional Data Base, 2017

Table 2. Distribution of Top Five Cancer Types Which Are Most Common in Females According to Data of Globocan 2020 Published by International Agency for Research on Cancer (IARC)

	Turkey*	**World**	**Western Asia**	**Central and Eastern Europe**	**USA**
1	Breast	Breast	Breast	Breast	Breast
2	Thyroid	Colorectal	Thyroid	Colorectal	Lung
3	Colorectal	Lung	Colorectal	Uterus Corpus	Colorectal
4	Lung	Uterus Cervix	Lung	Lung	Uterus Corpus
5	Uterus Corpus	Thyroid	Uterus Corpus	Uterus Cervix	Skin Melanoma

* Turkey Compositional Data Base, 2017

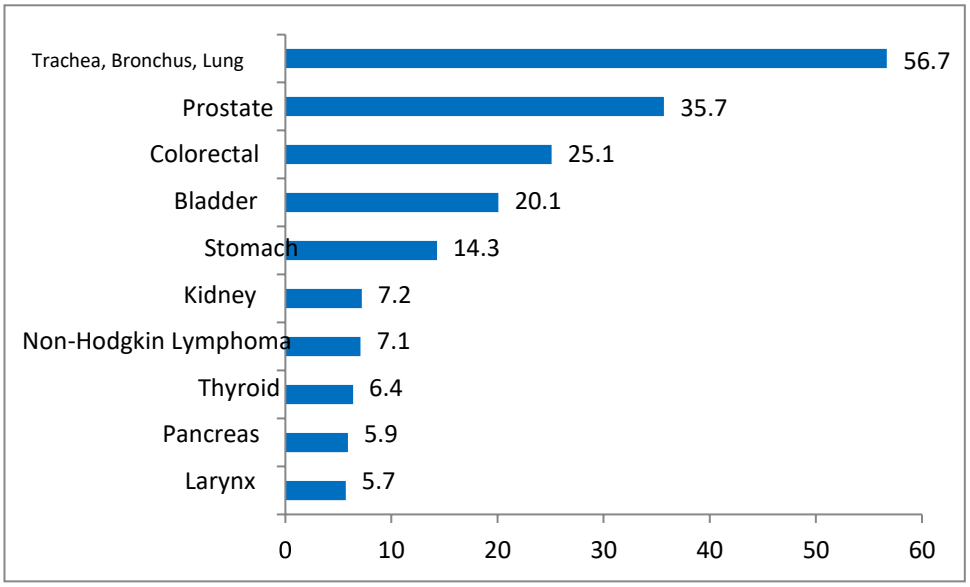


Figure 3. Age-Standardized Rates of 10 Cancer Types Which Are Most Common in Males (Turkey Compositional database, 2017) **(**World Standard Population, per 100,000 individuals**)**

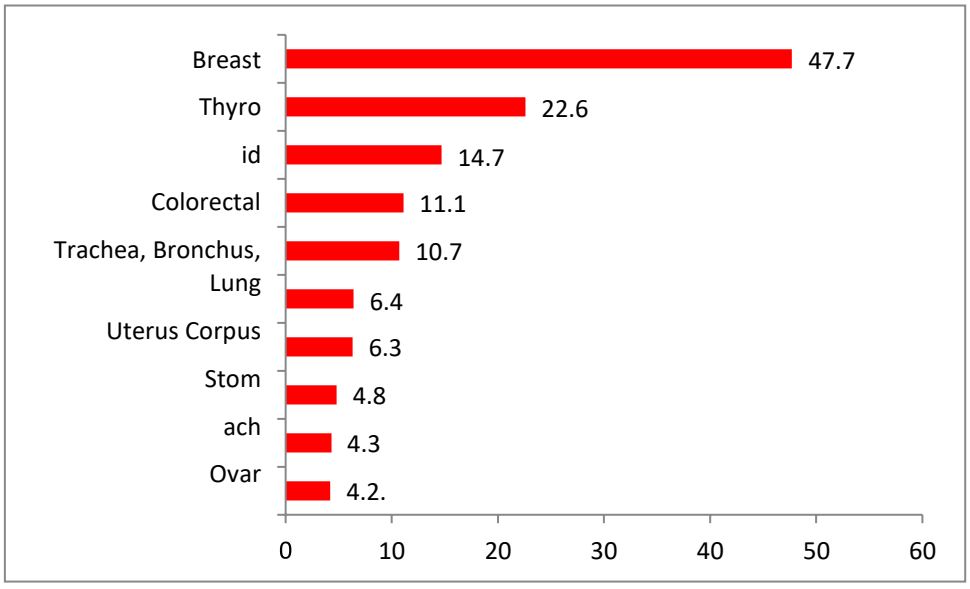


Figure 4. Age-Standardized Rates of 10 Cancer Types Which Are Most Common in Females (Turkey Compositional database, 2017) (World Standard Population, per 100,000 individuals)

Turkey general cancer incidence is at a lower rate when it is compared with the developed countries such as European Union countries and United States of America (Figure 5). However, when lung cancer incidence, which ranks first especially in males in our country, compared to mentioned countries' lung cancer incidences, it is seen that this type

of cancer is much more common in our country. Among the aforementioned countries, in our country where the tobacco use is high, it is thought that lung cancer is more common in parallel with this fact [7].

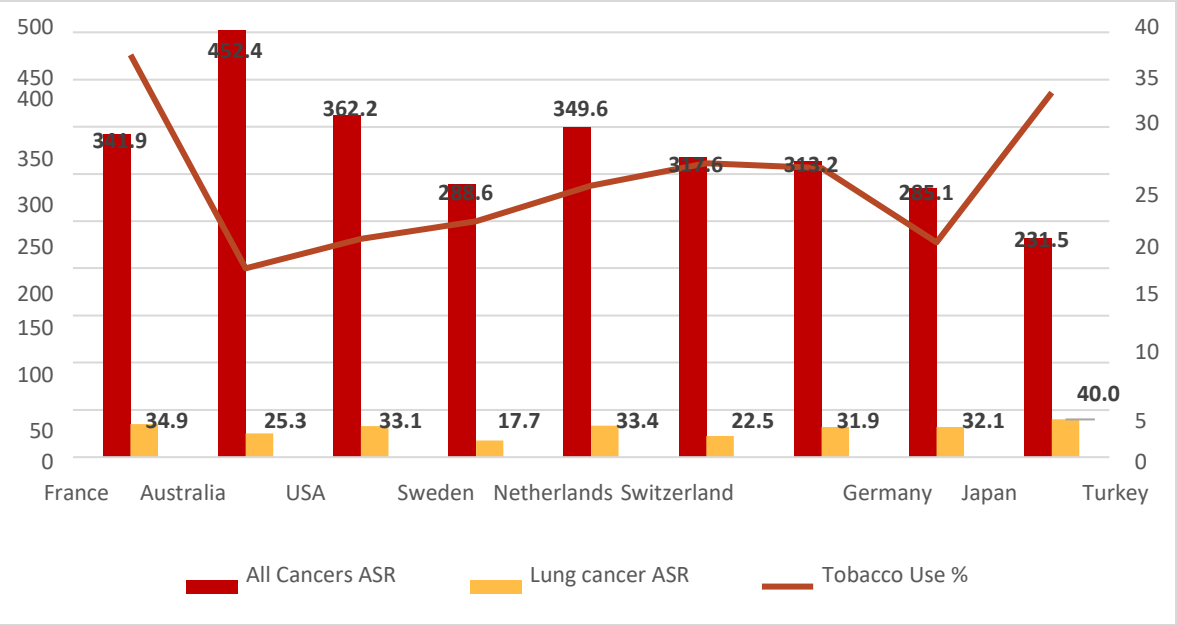


Figure 5. Age-Standardized Rates and Percentages of Tobacco Use for All Cancers and Lung Cancer in Some Countries, GLOBOCAN 2020

Changing or preventing major risk factors may significantly decrease the cancer burden. Risk factors in question include these;

- Tobacco use, including cigarettes and smokeless tobacco products
- Being overweight or obese
- Malnutrition that includes low intake of fruits and vegetables
- Insufficient physical activity
- Alcohol use
- Sexually transmitted Human Papilloma Virus (HPV) infection
- Exposure to hepatitis or other carcinogenic infections
- Exposure to ionizer and ultraviolet radiation
- Urban air pollution
- Indoor smoke that stems from usage of solid fuel [1].

In addition to these measures, early diagnosis and treatment is possible by conducting

proper programmes in some cancers as is the case with breast, cervical and colorectal cancers. The vast majority of breast, cervical and colorectal cancers can be detected at the level of localized and regional rates through cancer screening programme conducted in our country (Figure 6).

According to available data of 2017 Turkey SEER (The Surveillance, Epidemiology, and End-Results) Summary Staging which is developed to be used in Cancer Registry Centers by the US National Cancer Institute and to guide the cancer registrar in interpreting the prevalence of the disease based on medical records, it is seen that 63% of cervical cancers are Stage 0, 51% of breast cancer in females are Stage 0-1, 36% of colorectal cancers are Stage 0-1 (Figure 6). (At this point, the fact that cervical cancer screening rate is higher than other screening cancers can be interpreted as the result of a higher early stage detection rate in this cancer type.)

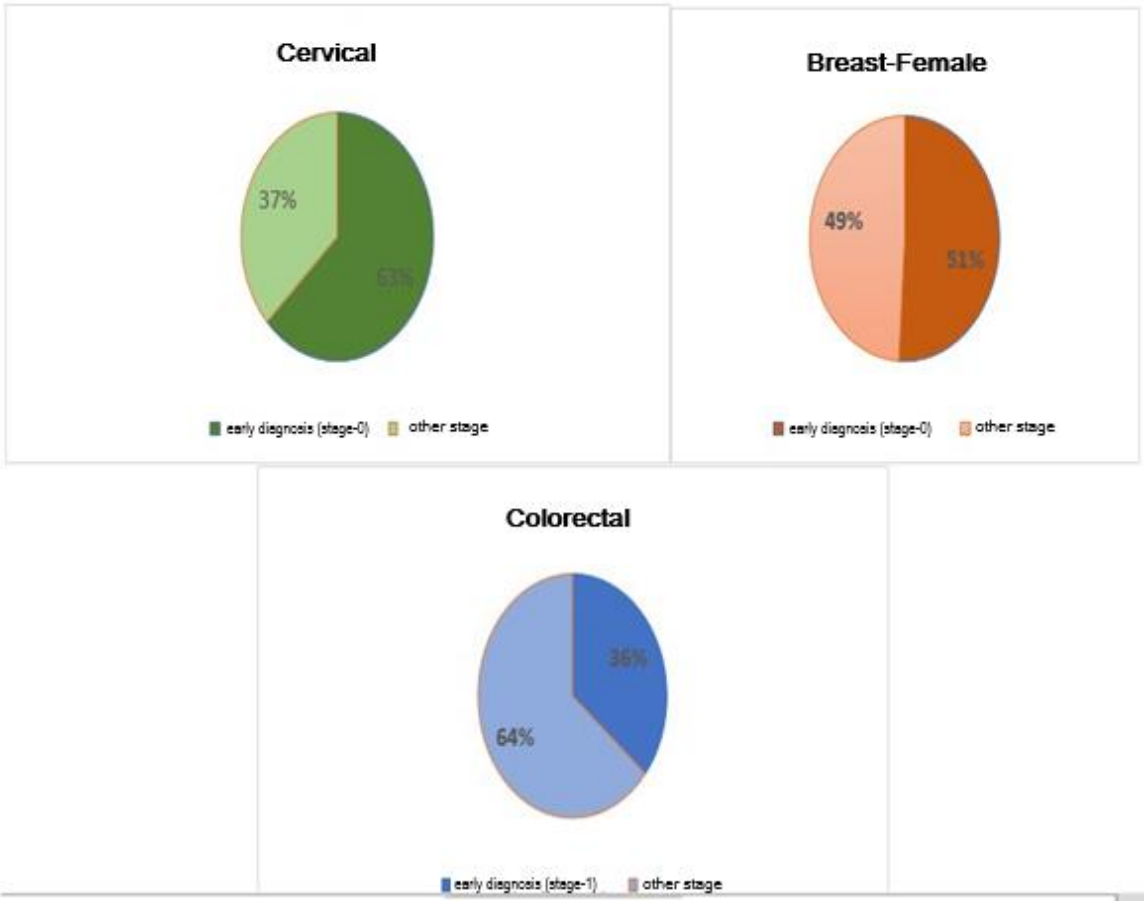


Figure 6. SEER Summary Staging Distribution of Screening Cancers (Turkey Compositional Data Base, 2017)

Palliative/supportive care is defined as the health service that starts after the diagnosis of cancer and provided to eliminate the problems experienced by patients and their families and to improve their quality of life during the treatment. While palliative care is the service provided at all stages of the disease, it is a type of care that meets necessities especially in the period that requirements of patients and their families are increased at the advanced stage of cancer. The aim of palliative care is relieving the pain and other symptoms of patient, nutritional support, giving psychological and social supports, ensuring patient's comfort and care, training patients and their families, focusing on improving the functional status of patient and this mentioned care service is provided by a multidisciplinary team that is formed by different occupational groups [8].

The palliative treatment should be provided in the best possible way in order for all patients diagnosed early or late to have a quality life and longevity and to treat the disease at an optimal level in effective cancer control. A national cancer control program is required that takes care of national sources and needs in order to conduct all these measures as part of a specific plan.

In this regard; it is very important to present the problems on a national scale, to improve the national screening program within the bounds of possibility and to implement it throughout the country by taking into consideration regional differences.

Consequently, data of countries should be evaluated one by one in terms of the socio-cultural features, human resources and financial resources in order to implement cancer control steps effectively that are accepted all over the world, the work to be done should be prioritized and most importantly an accepted national program should be composed with the participation of all practitioners. Full and effective control of cancer, which is one of the most important public health problems of the era, can only be possible with a dynamic, versatile, scientific, multidisciplinary and cost-effective program.

Development Stages of Turkey National Cancer Control Programme (NCCP)

Our Ministry is in cooperation with a vast number of national and international institutions and organizations in order to follow up scientific developments and good practices in the world on cancer control and to set an example for some countries in this respect;

1. WHO (The World Health Organization)
2. IARC (International Agency for Research on Cancer)
3. IACR (The International Association of Cancer Registries)
4. UICC (The Union for International Cancer Control)
5. NCI (The National Cancer Institute)
6. APOCP (The Asian Pacific Organization for Cancer Prevention)
7. MECC (The Middle East Cancer Consortium)
8. NHS (The National Health Service)
9. ENCR (The European Network for Cancer Registries)

This program, which is intended to guide all internal and external stakeholders by bringing it into a written document with the participation of prominent scientists of all interested parties in cancer control and our country, was prepared in cooperation with T.R. Ministry of Health GDPH Head of Department of Cancer and The World Health Organization (WHO).

The priorities which are aimed at cooperation between WHO Regional Office for Europe and T.R. Ministry of Health were regulated in accordance with two-year cooperation agreement signed between Turkey and WHO Regional Office for Europe. According to the Cooperation Agreement signed on 2008-2009, five priorities were determined “to develop policies for non-communicable diseases by Ministry of Health and to strengthen the capacity for implementation”. These are; cancer control, prophylaxis, palliative care, obesity prevention and tobacco control.

WHO, together with Ministry of Health, organize and finance workshops to create a National Cancer Control Programme (NCCP) (Figure 7,8) to reduce cancer-related deaths and to increase the quality of life for cancer patients through implementation of evidence-based strategies for prevention, early detection, diagnosis, treatment and palliation by enabling use of current resources of WHO in the best manner with participation of expert organizations and individuals on this issue.

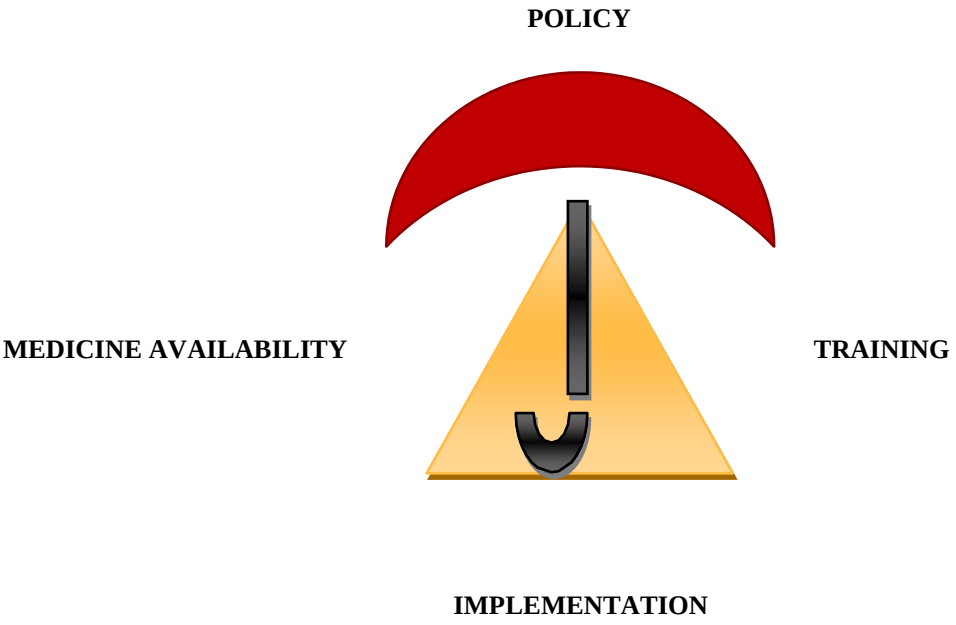


Figure 7. WHO Strategies for National Cancer Control Programme: Establishing Standards

Figure 8. National Cancer Control Programme

The first phase of Turkey Cancer Control program was carried out between 2008 and 2012, the second phase was conducted between 2013 and 2018. The third phase of the program was created through experiences during the aforesaid process and under the light of new international scientific data by consulting with our national consultation boards for cancer as well as many active international organizations and institutions (WHO, IARC, European Union Scientific Commission) (2019-2023).

Principals of a National Cancer Control Programme

A comprehensive National Cancer Control Programme (NCCP) performs cost-effective studies including majority of the population to control the cancer. Putting emphasis on the cancer control programs, early detection and treatment of the cases, improving treatment guidelines enable high quality of life as much as possible for the patients at advanced stage as cancer control.

National Cancer Control Programmes are designed in accordance with the socioeconomic and cultural structures of the countries. These programmes help policy makers and program directors to use the current resources efficiently

to develop a sufficient, fair, sustainable and reproductive strategy. National Cancer Control Programmes should be carried out step by step by identifying and undertaking the most preemptors and most beneficiaries.

From the point of WHO, within the integrated Public Health National Cancer Control Programme; "Framework Contract for Fight against Tobacco", "Global Diet Strategy", "Physical Activity and Health" are very important to struggle with non-communicable diseases and global epidemics of cancer. These are the most important causes for death today. Every year, 40 millions of 57 millions deaths result from noncommunicable diseases. 37% of the deaths related to non-communicable diseases occur
in low income countries whereas 88% appear in medium and high income countries [9].

Our National Cancer Control Programme comply with the control programmes prepared and conducted by other departments of our ministry and include counteracting plans with relevant chronic diseases beside cancer.

For instance, "Turkey Obesity Control Programme", "Tobacco Control Programme" and "Diabetes Control Programme" have an association with each other. National Cancer Control Program includes many institutions and organizations. Although prevention, screening and palliative care are the most significant investments, the program does not appear solely, but also include wider health reforms. Healthy maintenance of the services is possible by working in cooperation with Family Practice System which has been established within the scope of Health Transformation Programme in Turkey. When the extent of target population is considered, the importance of such integration would be understood better.

National Cancer Control Programme can reach its aims by covering every segment of society and carrying out the necessary intervention studies for target groups.

RESOURCES

1. Cancer Key facts 12 September 2018. WHO. https://www.who.int/en/news-room/fact-sheets/detail/cancer (Date Accessed: October 9,2019)
2. TSI. Causes of Death Statistics, 2016.http://tuik.gov.tr/PreTablo.do?alt_id=1083 (Date Accessed: October 9,2019)
3. https://gco.iarc.fr/today/home (Date Accessed: August 12, 2019)
4. World Cancer Report 2008. Ed: Boyle P, Levin B. International Agency for Research on Cancer, Lyon, France 2008.
5. World Health Organization. Cancer Fact Sheet February 2018. http://www.who.int/en/news-room/fact-sheets/detail/cancer Date Accessed: June 5, 2018
6. T.R. Ministry of Health, General Directorate of Public Health (2018) Turkey Cancer Statistics 2017, Accessed from https://hsgm.saglik.gov.tr/depo/birimler/kanser-db/istatistik/Turkiye_Kanser_Istatistikleri_2017.pdf on August 12, 2021.
7. WHO (2017) Who Report on the Global Tobacco Epidemic, Monitoring tobacco use and prevention policies.
8. Preface Palliative Care for Cancer Patients and Their Families Ed: Özçelik H, Fadıloğlu Ç, Uyar M, Karabulut B. Izmir, 2010. s.x
9. http://www.onkoloji.gov.tr/attachments/article/8575/kanser-hastalari-ve-aileleri-icin-palyatif-bakim-kitabi_01.pdf(Date Accessed: December 9, 2019)
10. World Health Organization. The top 10 causes of death May 2018 World Health Organization. February 15, 2019 accessed from https://www.who.int/news-room/fact-sheets/detail/the- top-10-causes-of-death .

SECTION 1

CANCER REGISTRATION

1. CANCER REGISTRATION

Cancer registration is all the procedures of collecting information about all cancer cases that occured in a specific population and documentation of this information with the clinical and pathological indicators of cancer. There are different registration systems. The aim of population-based active cancer registration system, which is conducted by our ministry, is collecting information about cancer cases observed in our society. This system is the golden standard for finding cancer incidences in a specific population [1,2].

Cancer registration ensures vital contributions to cancer control by several ways from identifying cancer burden and geographic range to understanding the causes for cancer, from population-based survival analyzes to evaluating the diagnosis, treatment and nursing quality of cancer. In case there is not reliable cancer registry data, cancer control will go in the wrong direction and national resources will be squandered [2].

When data of developed and developing countries are reviewed, it is seen that incidences and profiles of cancers differ among the countries. For instance, cancer incidence in Turkey is higher than the cancer incidence in the world. Average cancer incidences in Western Asia Region which includes our country are also lower than the average cancer incidences in Turkey (Table 1.) [3,4].

Table 1. Status of Turkey According to Data of Globocan 2020 published by International Agency for Research on Cancer (IARC) (Age Standardized Rates/ per 100.000 individuals)

	Male*	**Female***
World	222.0	186.0
Western Asia	198.3	162.3
Central and Eastern Europe	293.8	220.9
USA	400.9	333.2
Turkey**	259.2	187.0

*Age-Standardized Rates per 100.000 individuals ** Turkey Compositional Data Base, 2017

On the other hand, it is seen that cancer incidences for some cancer types in developed countries such as Northern Europe and United States are higher than the cancer incidences in Turkey. **In Africa Region, high rates of cervical cancer especially in females stand out.** Thyroid cancer frequency in females is higher than it is in males, and thyroid cancer incidence increases prominently in several regions of the world (Figure 1.1, Figure 1.2) [3,4]. In order to evaluate this situation, "Thyroid Cancer Report in Turkey and around the World" was published by our Department in 2016. In the report, female gender, obesity, iodine deficiency and radiation exposure in childhood were explained as etiological causes that are relevant to thyroid cancer. In the report (as many international studies have shown); it is emphasised that increase generally is seen at early stage; however, there may not be a real increase due to the fact that deaths from this cancer do not increase [5]**.**

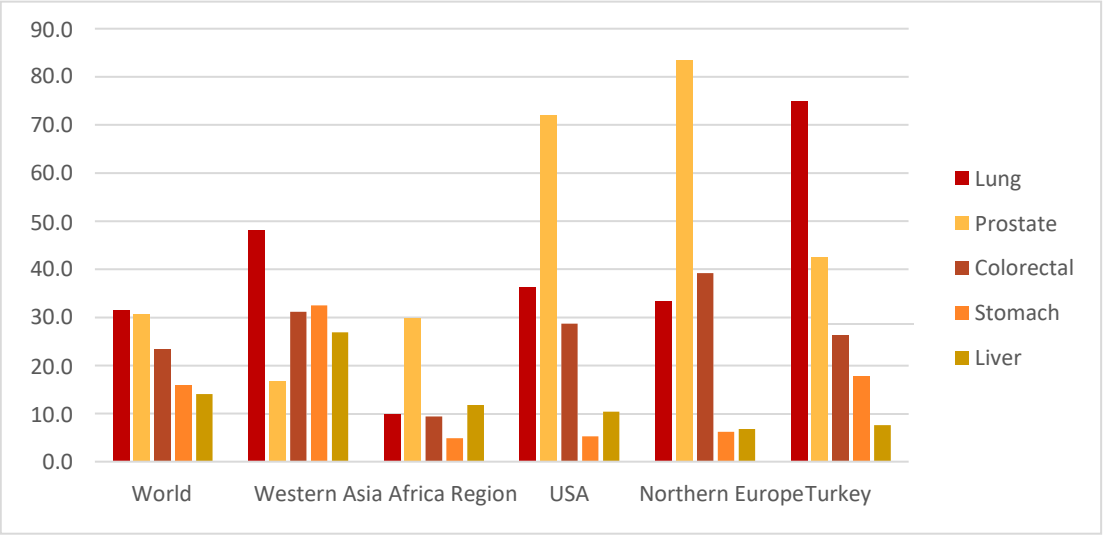


Figure 1.1. Age-Standardized Rates of 5 Most Common Cancer Types in Males by Region, in the World, per 100,000 individuals (GLOBOCAN 2020)

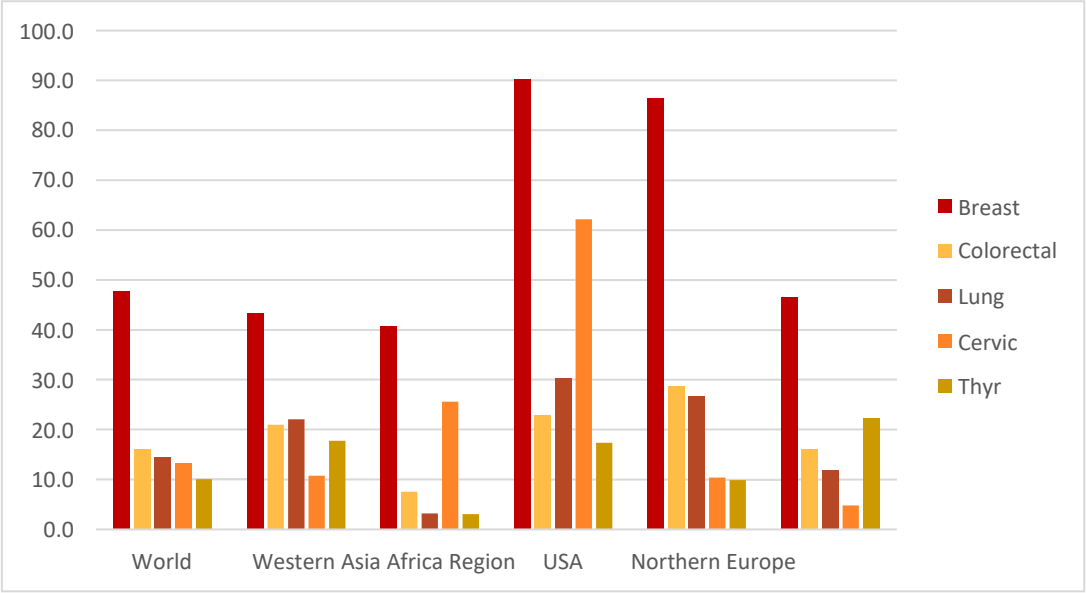


Figure 1.2. Age-Standardized Rates of 5 Most Common Cancer Types in Females On the Basis of Region, in the World, per 100,000 individuals (GLOBOCAN 2020)

1.1. Cancer RegistrySystem in Turkey

Although institutionalization of cancer registry activities in Turkey, where the history of cancer registration activities is not old, has started in 1940s, it can be said that efforts of cancer control has started by including the cancer into notifiable diseases which were set out in Article 57 of Public Health Law numbered 1593 in 1982, according to Ministry Circular numbered 5621 and dated 14.09.1982 On the global scale, Hamburg Cancer Registration was founded in 1926 and had a legal status in 1929. This organization became a completely operational population-based cancer registration in 1937. Furthermore, the cancer registry system in Slovenia publishes the incidence, prevalence and survival rates since 1950. As can be seen from these examples, cancer registration activities has started at early 1900s in many developed countries on a global scale.

Through enforcement of mandatory cancer notification, a “Department of Cancer Control” was founded in 1983 by the Decree Law No. 181 to carry out cancer registration activities. One of the basic tasks of Fight against Cancer Department is to collect qualified cancer records reliably and correctly. Turkey became a member of The International Association of Cancer Registries (IACR) in 1989.

When enough and quality data cannot collected in cancer registration that started with passive system, in 1992, collection of cancer registrations started with active system and for the first time active cancer registration center was established in Izmir within the scope of "Cancer Registration and Incidence Project". Antalya Cancer Registration center started cancer registry actively in 1998 (Table 2).

Table 2. Cancer Registry Centers and Reference Dates in Turkey

	Provinces	**Reference Year**
1	Izmir	1992
2	Antalya	1998
3	Bursa	2000
4	Eskişehir	2000
5	Samsun	2001
6	Trabzon	2003
7	Edirne	2004
8	Erzurum	2005
9	Ankara	2006
10	Kocaeli	2007
11	Gaziantep	2010
12	Malatya	2010
13	Mersin	2012
14	Istanbul	2012

A “Regulation for Cancer Registration Center” was enforced in 2000. Turkey became an official member of Middle East Cancer Consortium (MECC) in 2004, the activities started to be in collaboration with MECC.

National Cancer Consultative Committee and Department personnel reviewed the Active Cancer Registration System in 2006. By decision of Sub Committee of Cancer Epidemiology and Cancer Registration Consultation **dated 05.01.2006**, the cities which kept qualified records with too little intervention were identified to provide efficient use of the resources and to get results within the shortest period of time through review of the activities of the cities within the frame of active cancer registration system. In this context, training/supervision activities onsite were performed in Ankara, Izmir, Erzurum, Edirne, Eskisehir, Samsun, Trabzon, Antalya, Bursa centers and providing a more efficient

monitoring of the studies was decided; it was seen that the population of the aforesaid 9 cities created about 23% of our population.

The data of cancer registry centers can give a place on "Cancer Incidence on Five Continents" book published by International Agency for Research on Cancer (IARC) only if they pass quality assessments. Although, in our country, cancer registry started in 19922, incidence report formed from the data from active centers was published for the first time in the 2002 series. The data from Izmir and Antalya Cancer Registry Centers (1998-2002 series) were included in the Ninth Edition of "Cancer Incidence on Five Continents Book" [6] whereas the data from 2003-2007 series of Trabzon and Kayseri Cancer Registry Centers were included in the tenth edition of the same book [7]. Bursa, Erzurum, Eskişehir, and Samsun provinces were included and the number of provinces included in the report from our country reached 8 on the eleventh edition of "Cancer Incidence on Five Continents Book" [8]. The number of provinces with enough quality of cancer data that were included in Turkey Cancer Statistics Report has increased over the years and reached 14 (Izmir, Antalya, Bursa, Eskişehir, Samsun, Trabzon, Edirne, Erzurum, Ankara, Gaziantep, Malatya, Istanbul, Mersin ve Kocaeli) and Turkey Cancer Statistics 2017 was presented to involve 50.3% of the country-wide (Table 3) [4].

Table 3. Distribution of Years That Active Cancer Registry Centers Were Reported in Turkey

	2013	2014	2015	2016	2017
Izmir	√	√	√	√	√
Antalya	√	√	√	√	√
Bursa	√	√	√	√	√
Eskişehir	√	√	√	√	√
Samsun	√	√	√	√	√
Trabzon	√	√	√	√	√
Edirne	√	√	√	√	√
Erzurum	√	√	√	√	√
Ankara	√	√	√	√	√
Gaziantep	√	√	√	√	√
Malatya	√	√	√	√	√
Istanbul	√	√	√	√	√
Mersin	√	√	√	√	√
Kocaeli				√	√
TOTAL	13	13	13	13	14
Population in the sample	36.463.691	37.049.219	37.717.263	40.048.173	40.651.792
Total population	76.667.864	77.695.904	78.741.053	79.814.871	80.810.525
% of total population	47.5	47.7	47.9	50.2	50.3

Studies were started to provide a data flow from all regions of our country in 2012 and the number was gradually increased up to 81 in 2013.

In our country there are three more provinces that gather data with active cancer registry system apart from nine provinces that are approved in terms of quality and complement of cancer data. These provinces are Gaziantep, Kocaeli and Malatya. Istanbul, Mersin and Adana were included to these provinces in 2012. Population comprehensiveness reached to approximately 50% by including Gaziantep, Malatya, Istanbul, Mersin provinces, which are considered to have enough quality among these provinces, to the report. Turkey Cancer Statistics 2017 was presented with 53% comprehensiveness by including Kocaeli province.

Cancer survival in five continents is evaluated through CONCORD which is the programme for world-wide surveillance of trends in cancer survival, led by the London School of Hygiene and Tropical Medicine. The CONCORD programme is endorsed by 40 national and international agencies, including WHO EURO, the Organisation for Economic Co-operation & Development (OECD) and the World Bank. Data and survivals of 18 cancer types from 322 population-based cancer registry centers in 71 countries were published in Global Surveillance of Trends in Cancer Survival 2000–14 (CONCORD-3). The data from 9 cancer registry centers in our country (Ankara, Antalya, Bursa, Edirne, Erzurum, Eskişehir, Izmir, Samsun and Trabzon Cancer Registry Centers) are also included in the mentioned publication [9].

By these gathered data it has been aimed to calculate incidences relating to cancer types, to determine the distribution of these incidences according to age groups, gender and regions; to put forward thesis that will be mentioned for new search about cancer reasons peculiar to the region by evaluating the incidences that are lower or higher than expected , to constitute data base for scientific researches and to reach data that will provide cancer protection.

In recent years these activities conducted by our Department have been increased and studies about forming a strong registry system, which is the first step of cancer control, are still continuing.

"Cancer Notification and Cancer Registry Centers Regulation" was published in the Official Gazette in June 3, 2015. Once the regulation was published, Cancer Registry Circular that is drafted in 2019 about implementation of regulation was issued to all health institutions and organizations.

T. R. Within the scope of Ministry of Health Certified Training Programme, the "Cancer Registrar Certified Training Programme" entered into force with the approval of the Ministry dated May 24, 2017.

Within the framework of the Cancer Registrar Certified Training Programme;

- ✓ The personnel that are assigned in these provinces take "Basic Cancer Registry Education" during which basic information about cancer epidemiology and cancer registry are given,

- ✓ “Can Reg Computer Program Education” to provide the transfer of data used in cancer registry to digital environment, to provide data storage and to make the quality control of data,
- ✓ “SEER Summary Staging Education” is given to search the prevalence and nature of cancer, to evaluate the effectiveness of treatment, to gain skills about using criteria such as measuring of survival.

T.R. Ministry of Health Head of Department of Cancer is the member of international organizations such as WHO (The World Health Organization), IARC (The International Agency for Research on Cancer), MECC (The Middle East Cancer Consortium), IACR (The International Association of Cancer Registies), ENCR (The European Network For Cancer Registries) ve UICC (International Union Against Cancer), NCI (The National Cancer Institute), APOCP (The Asian Pacific Organization for Cancer Prevention), NHS (The National Health Service) and also attends to the conferences and meetings organized by these organizations about cancer registry and it contributes to educational studies. Obtaining accurate cancer data which is the most important and first phase of cancer control program has been considered more importantly in recent years and the quality of our data have been increased.

1.2. Active Cancer Registry Activities Conducted in Turkey

Operation diagram below was applied in active registry activities conducted in 81 provinces.

- Firstly, relevant health management authorities of each province were informed. Information campaign started from Governorship. Administration support for the subject was received.
- The population, the situation of hospital and other sources of each province were evaluated and the necessity of cancer registry personnel were identified.
- By taking into consideration the experiences of Center of Cancer Registry of Izmir, Standard Training Programmes within the scope of IARC and MECC standards were formed.
- Cancer Registry Form to be used was revised.
- Personnel trainings were performed.

- During the visits to provinces, problems resulting from the provincial administration or hospital administration were tried to be identified and worked out.
- First Diagnosis Date, Histological Type and Parameters of Location of Tumor were obligated in Cancer Data Set within the Information Management Systems of Hospital.
- To invoice the CHP codes which have a sequence number of 4724 in Health Instutions Point List and whose process name is included in the 9.7 Pathology (Cytologic Materials, Histopathologic Research, Specific Pathologic Investigations and Electron Microscopic Examinations), and in order to ensure that they are included in the Hospital Information Management Systems, Pathology Registration Package submission was started to be controlled on the basis of repayment with SSI effective from the date of August 1, 2019.
- In 2019, quality control in provinces was completed, data repository was formed with 2017 data and Turkey Cancer Statistics Report was prepared by processing these data (interprovincial duplication control, quality control, etc.) and analyzing them.
- The headship has started the study of quality control of 2018 data and it is planned that relevant statistics is going to be published by the end of 2021.

1.2.1 Data Gathered by Active Cancer Registry System

Demographical Data:

1. Name(s): Name, Surname, Father's Name
2. Address, Street and Province that are valid in the date of diagnosis
3. Place of Birth
4. TR identity number
5. Age during diagnosis
6. Date of Birth
7. Gender Medical Data:

• Date of diagnosis:

1. It is used to determine the incidence year and survival period.
2. It is the date when the doctor explains that the patient is cancer patient.

• Diagnosis Method:

1. Anatomical (topographic) location
2. Histological (morphologic) type
3. Behaviour
4. Degree
5. Laterality
6. Tumor row
7. Stage during diagnosis

• Treatment data:

1. Surgical operation
2. Radiotherapy
3. Chemotherapy
4. Hormone therapy
5. Immunotherapy
6. Other therapies
7. Date(s) of treatment
8. Order of surgical operation and radiation

1.2.2 Data Sources in Active Cancer Registry System

• The places where medical records are kept;

- Hospitals
- Clinics
- Doctor's clinics
- Pathology laboratories
- Radiation (oncology) therapy centers

- The places where medical records are kept;
  - Medical oncology centers
  - Dispensaries
  - Forensic medicine centers
- Death certificates

1.2.3. Quality Control in Active Cancer Registry System

To get the accurate results about cancer burden in given population, accurate and complete cancer registry data are needed.

1. Comparability

Statistics that are made by cancer registry center must be comparable for different societies and/or different time periods. Basic precondition of comparability is to pick up on universal standards and rules. Data terms and relevant terms must be identified clearly, guide for "rules and definitions" must be prepared and changes must be documented.

- ✓ Data elements that will be gathered,
- ✓ Inclusion of the incident into database,
- ✓ Date of diagnosis,
- ✓ Method of diagnosis,
- ✓ Multiple primer,
- ✓ Location of primer,
- ✓ Stage of disease, etc.
- ✓ The use of the data and information (confidentiality) must be included in this document.

Guides used for the setting of the rules:

- ✓ **WHO / IARC / IACR** (The World Health Organization / International Agency for Research on Cancer / The International Association of Cancer Registries)
- ✓ **ENCR** (The European Network for Cancer Registries)
- ✓ **SEER** (Surveillance, Epidemiology and End Result, Dept)
- ✓ **MECC** (The Middle East Cancer Consortium)

2. Completeness

It refers to the extent of all cancer cases emerged in target population are included in the database of cancer registry center.

Completeness control on the database can be in two ways:

- Determination of the frequency of diagnosis with histological confirmation: The fact that the frequency of diagnosis with histological confirmation in the data base is 100% shows cases that diagnosed with presumably clinical, laboratory and screening methods and that should not be surgically intervened are missed. For this reason, it is not a desired situation.
- Evaluation of changes in incidence rates in time: Sudden increases and decreases are not anticipated in cancer incidence rates unless there is an extraordinary intervention (initiation of screening program, change in registration, etc.). However, it takes time for incidence rates to catch up the social dynamics especially in centers that has started cancer registration recently. Therefore, durableness is significant for successful cancer registry in cancer registration centers [10].

3. Validity

It is the fact that the data collected represents the circumstance as in reality. Validity control through the database can be in two ways:

- Determination of the imperfect data frequency
- Evaluation of the diagnosis methods

As to the "evaluation of diagnosis methods" from these methods a linear relationship is available between frequency of diagnosis with histological confirmation and validity [11].

1.3. Reliability in Cancer Registry System and Quality Control Evaluations

In Turkey, quality control and reliability of information in cancer registry system are made with the methods that are determined by IARC. In order to use the data confidently, obtained from 14 provinces that represents 50.3% of Turkey, data reliability and quality control system started to be operated in these provinces too. Izmir, Antalya, Ankara, Bursa, Samsun, Trabzon, Eskisehir, Edirne, Erzurum, Gaziantep, Malatya, Istanbul, Mersin,

Kocaeli are the provinces where data reliability and quality control system are made in detail according to the criteria of IARC.

These provinces give examination and evaluation reports regularly to the Department of Cancer. These reports include information about general situation, personnel, data and physical conditions of cancer registry center. Data analysis about control studies of cancer registry is included in these mentioned reports. At cancer registry centers, data are evaluated under 5 basic titles.

1. Completeness of cover of data resources
2. Completeness of detail of cases obtained from resources
3. Reliability and accuracy of detail
4. Accuracy of reporting
5. Accuracy of interpretation and evaluation of data and data resources

Evaluations are also being made of the provinces that have joined the active registration system in recent years, studies to include the provinces in the report, that reach the suitable level, have been continuing.

The compliance of these provinces with quality standards is evaluated as to whether there are major and minor defaults.

- Evaluation process of major inconsistencies:

1. Inconsistencies between gender and location of tumor
2. Inconsistencies between histology and locations of tumor
3. Inconsistencies between date of diagnosis and date of birth
4. Inconsistencies between last control date and date of diagnosis
5. Inconsistencies between vital situation and date of diagnosis and last control date
6. Inconsistencies between histology and diagnosis method
7. Inconsistencies between behavior codes

- Evaluation process of major inconsistencies:

1. Permissible time intervals at deviations in the date of diagnosis are evaluated.

2. When calculating the age at the time of diagnosis and when calculating the date of diagnosis, month errors resulting from the transfer of the month are evaluated. Although the date of birth of the patient is known, age errors, resulting from not knowing the exact month/day, are corrected.

3. While coding the place of birth and address, the province is recorded correctly but errors that may occur resulting from the records of district, village, township etc. are evaluated.

4. Summary stage during diagnosis (SEER) is evaluated.

Re-availability of data, data leakage and its convenience for detection of repetitions are evaluated by controlling file archiving system at registry centers. Data are found from archive and all files are examined, reliability of data are evaluated, it is reported to the center

RESOURCES

1. Cancer Registration in Turkey T.R. Ministry of Health Head of Department of Cancer Control Ankara, 2011.p.12
2. Bray F, Znaor A, Cueva P, et al. Planning and Developing Population-Based Cancer Registration In Low- And Middle-Income Settings. IARC Technical Publication No. 43. International Agency for Research on Cancer. France,2015. p. vii-3. http://publications.iarc.fr/Book-And-Report-Series/Iarc-Technical-Publications/Planning-And-Developing-Population-Based-Cancer-Registration-In-Low--And-Middle-Income-Settings-2014 Erişim Tarihi: 08.06.2018)
3. Ferlay J, Ervik M, Lam F, et al (2018). Global cancer observatory: cancer today. Lyon, France: International Agency for Research on Cancer. Available from: https://gco.iarc.fr/today/home Date accessed: August 26, 2019
4. T.R. Ministry of Health, General Directorate of Public Health, Head of Department of Cancer, 2017 Turkey Cancer Statistics
5. Head of Department of Cancer Thyroid Cancers, Thyroid Cancers in the World and Turkey Report No: 5, Ankara, 2012.
6. Curado. M. P., Edwards, B., Shin. et al.eds (2007) Cancer Incidence in Five Continents, Vol. IX.IARC Scientific Publications No. 160, Lyon, IARC
7. Forman D, Bray F, Steliarova-Foucher E, et al (2012). Cancer Incidence in Five Continents, Vol. X. Remote Address:http://ci5.iarc.fr/CI5-X/ci5-X.htm Date Accessed:

January 10, 2013.

8. Cancer Incidence in Five Continents, Vol. XI (electronic version). Lyon: International Agency for Research on Cancer. http://ci5.iarc.fr/CI5-XI/Default.aspx Date Accessed: February 28, 2018
9. Allemani C, et al. Global surveillance of trends in cancer survival 2000–14 (CONCORD-3): analysis of individual records for 37 513 025 patients diagnosed with one of 18 cancers from 322 population-based registries in 71 countries. The Lancet. Published online January 30, 2018 http://dx.doi.org/10.1016/S0140-6736(17)33326-3 (Date Accessed: February 8, 2018)
10. Anton-Culver H, Young JL Jr (eds). Standard Operating Procedures for MECC Cancer Registry Centers Translation Ed.: Eser S, Yakut İC, Özalan S, Karakılınç H. Ankara, December 2008.
11. Young JL Jr, Ward KC (eds). Handbook for Cancer Registration Standards Translation Ed.: Eser S, Ozalan S. Ankara, 2013.

SECTION 2

THE MOST COMMON ADULT AND CHILDHOOD CANCER TYPES IN TURKEY

2.1. Trachea, Bronchial and Lung Cancers

Tracheal Tumors

Tracheal tumors are quite rare. Annual incidence was notified as 0.1 per hundred thousand, tracheal cancers are less than 0.5% of all malignant tumors [1]. 578 cases were notified in wide series reported within 31 years period. In this series, it was notified that average age was 63 and 56% of cases were males [2].

The vast majority of tracheal tumors stem from direct invasion of lung, esophagus, laryngeal, or thyroid tumors rather than primary. Rarely, hematogenous tracheal metastases may be seen in breast, colon, kidney, and melanoma.

2/3 of the primary tracheal tumors are squamous cell carcinomas, the second most common tumor is adenoid cystic carcinoma and these constitute 10-15% of all cases. Less common primary tracheal tumors are; mucoepidermoid carcinoma, non-squamous cell bronchogenic carcinomas, sarcomas, carcinoid tumors, pleomorphic adenomas and less common tumors [3, 4].

Squamous cell carcinomas, which is the most common type of primary tracheal malignant tumors, can show a multifocal outset in the ratio of 10%. Generally, it is initially observed as an intraluminal nodule, subsequently it can lead to the occurence of mediastinal direct invasion and lymph metastasis. It may cause tracheal stenosis and tracheoesophageal fistula [1].

Adenoid cystic carcinoma which is less common, also known as cylindrome, histologically resembles adenoid cystic carcinoma originating from salivary gland. It is a well-differentiated, slow growing tumor of tracheobronchial tree. Besides it features typically polypoid growth, an invasion on the cartilage structure can also be observed. Invasion is frequently observed on perineural and vascular structures. (5, 6).

Mucoepidermoid carcinoma (MEC) shows similarity with the MEC originated from salivary gland. Histopathologically squamous cells, contain mucin secreting cells and intermediary cells [5, 7]. Mucoepidermoid carcinoma is more commonly located in the bronchial glands and central airways than in the trachea. There are morphologically low and high grade types of it [5].

Clinic

Symptoms in tracheal tumors do not occur until %50 narrowing of the lumen diameter occurs. Symptoms vary depending on histologic type and localization of tumor. Squamous cell carcinomas frequently lead to hemoptysis complaint depending on mucosal irritation and ulceration. In the 6th and 7th decade of life, it is observed in those who often smoke as hoarseness and dysphagia [8].

Adenoid cystic carcinomas may often lead to wheezing and exertional dyspnea and less often hemoptysis. It is mostly observed in women and non-smokers. Low grade tumors such as mucoepidermoid carcinoma may be asymptomatic for years before diagnosis. Lesion is initially detected in the chest radiograph in 18-28% of tracheal tumors [9].

Diagnosis and Staging

The disease is generally diagnosed late since symptoms of disease may often be confused with clinical picture such as asthma, chronic obstructive respiratory disease, and pneumonitis. There is often no pathology in chest radiography and patients are often directed to treatment based on tomographic findings. Polypoid lesion, focal stenosis, eccentric narrowing or wall thickening are showed in trachea in tomography. At the next stage, fiberoptic bronchoscopy and biopsy are proper approaches to evaluate histological type of tumor, prevalence of it, suitability for surgery of the tumor (Image 1). Positron Emission Tomography (PET)/Computed Tomography (CT) is a vital approach in tumor staging, and in differentiation from benign etiology [10].

A staging system proposed by Surveillance, Epidemiology, and End Results (SEER) data base is suggested by some researchers while there is no staging system specified for tracheal tumors staging [11]. Specified staging system has a low survival prediction rate since it includes few patients and different histological tumors.

Treatment

Surgical resection is the appropriate treatment approach in proper cases in primary malignant tumor. The maximum length of resectable trachea in the surgical approach is notified to be 5 cm. Virtual, multidetector CT and fiberoptic bronchoscopy are appropriate methods to evaluate

the disease prevalence and suitability for resection. Limited resection and/or stenting via rigid bronchoscopy may be proper methods for pre-operative preparation [12].

In patients with a positive surgical margin and localized cases unsuitable for surgery, chemoradiotherapy is the appropriate approach. In cases with metastatic squamous cell carcinomas, systemic therapy may be a suitable approach. In cases with adenoid cystic carcinomas, there is no proof that chemotherapy changes the natural course of the disease. Therefore, observation is recommended in asymptomatic cases and if the patients are asymptomatic, they may be evaluated for palliative radiotherapy and/or chemotherapy [13, 14].

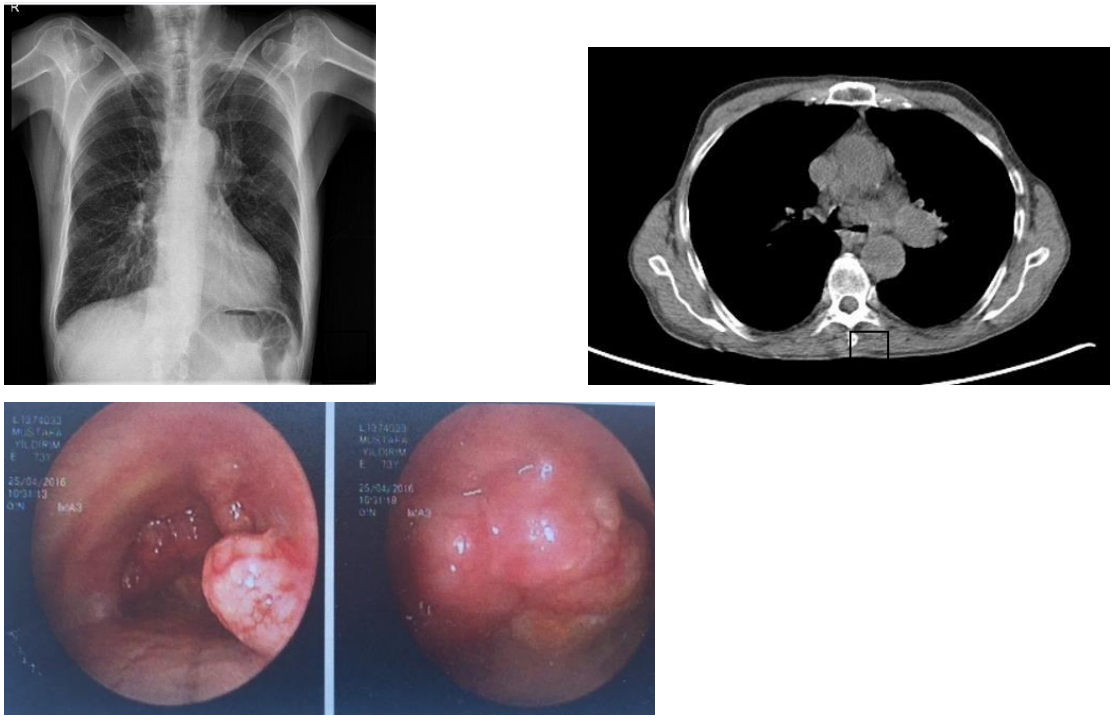


Image 1: Tracheal Squamous cell carcinoma A: Postero-anterior graphy of the case, B: Computed tomography view of the case C: Bronchoscopic view of the lesion of the case. It was taken from the archive of our clinic.

RESOURCES

1. Nouraei SM, Middleton SE, Nouraei SA, et al. Management and prognosis of primary tracheal cancer: a national analysis. Laryngoscope. 2014 Jan;124[1]:145-50.
2. Urdaneta AI, Yu JB, Wilson LD. Population based cancer registry analysis of primary tracheal carcinoma. Am J Clin Oncol 2011; 34:32-7.

3. Macchiarini P. Primary tracheal tumours. Lancet Oncol 2006; 7:83.
4. Ahn Y, Chang H, Lim YS, et al. Primary tracheal tumors: review of 37 cases. J Thorac Oncol 2009; 4:635.
5. Travis WD, Brambilla E, Müller-Hermelink HK, Harris CC. of the Lung, Pleura, Thymoma, and Heart. In: World Health Organization Classification of Tumors: Pathology and Genetics, IARC Presee, Lyon, France 2004.
6. Dean CW, Speckman JM, Russo JJ. AIRP best cases in radiologic-pathologic correlation: adenoid cystic carcinoma of the trachea. Radiographics 2011; 31:1443-7.
7. Molina JR, Aubry MC, Lewis JE, et al. Primary salivary gland-type lung cancer: spectrum of clinical presentation, histopathologic and prognostic factors. Cancer 2007; 110:2253.
8. Sherani K, Vakil A, Dodhia C, Fein A. Malignant tracheal tumors: a review of current diagnostic and management strategies. Curr Opin Pulm Med 2015; 21:322-6.
9. Wu CC, Shepard JA. Tracheal and airway neoplasms. Semin Roentgenol 2013; 48:354-64.
10. Park CM, Goo JM, Lee HJ, et al. Tumors in the tracheobronchial tree: CT and FDG PET features. Radiographics 2009; 29:55-71.
11. Bhattacharyya N. Contemporary staging and prognosis for primary tracheal malignancies: a population-based analysis. Otolaryngol Head Neck Surg 2004; 131:639-42.
12. Honings J, Gaissert HA, Verhagen AF, et al. Undertreatment of tracheal carcinoma: multidisciplinary audit of epidemiologic data. Ann Surg Oncol 2009; 16:246-53.
13. Gaissert HA, Grillo HC, Shadmehr MB, et al. Long-term survival after resection of primary adenoid cystic and squamous cell carcinoma of the trachea and carina. Ann Thorac Surg 2004; 78:1889-96.
14. Laurie SA, Ho AL, Fury MG, et al. Systemic therapy in the management of metastatic or locally recurrent adenoid cystic carcinoma of the salivary glands: a systematic review. Lancet Oncol 2011; 12:81524.

Lung Cancer Epidemiology

Lung cancer is the leading cause of cancer-related deaths all over the world. According to 2018 data of the World Health Organization (WHO), 2.09 million patients were diagnosed with lung cancer in all over the world and this figure constitutes 11.6% of all cancer types. The number of deaths related to this disease was notified as 1.76 million for the same year and constitutes the largest part of cancer related deaths, with 18.4%. [1]. The stated figures are substantially high by comparison the annual figures of 1.8 million cases

and 1.6 million lung cancer related deaths declared for 2012 [2]. Looking at the world data, lung cancer is the the most common and deadly cancer type in men and after breast cancer and colorectal cancer, it is the third most common cancer and the second most common cause of cancer related deaths in women
[3]. There are epidemiological differences based on countries. Cigarettes are the most important risk factor causing lung cancer development. In developed countries that fights well against smoking, lung cancer poses a problem below the world average in males and above the world average in females. For example, in the USA, lung cancer is the second common after prostate cancer in males and breast cancer in females. It ranks in the first place as the cause of death in both genders [4]. The global burden of lung cancer has been increasing and while this increase is much more distinct in male population, an increase in lung cancer incidence in female is notified. Significant differences are observed in lung cancer incidences and demographic data in developed and developing countries [5]. An increase in the lung cancer incidence is anticipated in parallel with the increase in the declared smoking prevalence in developing China, Indonesia, Eastern Europe, and North and East Africa [4, 6]. The highest smoking rates are notified from developing countries all over the world and more than half of lung cancer related deaths also occur in these regions [5].

While breast cancer is the leading cause of cancer related deaths in females, lung cancer ranks first in cancer mortality in North America, Southern/Western Europe, Australia and New Zealand. The high mortality rates reflect the high smoking rates [5, 6].

While it varies across countries, 48% of males and 10% of females smoke in all over the world according to data from WHO [7]. Smoking prevalance in females is lower in the developing countries compared to developed countries. In these countries, non-tobacco factors play a significant part in lung cancer development. In the studies conducted in the United States of America, the fact that a stable decline in smoking prevalence in both males and females since 1965 has presented, in case this trend continues, lung cancer mortality in females is expected to overtake the males in 2045 [8].

In our country, cancer registry is performed in a way that it includes 14 provinces in total and it includes 50.2% of the population. T.R. In the study conducted by Ministry of Health on these data, throughout Turkey, lung cancer is the most common cancer type in males and it ranks in the fourth place in females after breast, thyroid, colorectal cancers

(Figure 1,2)[9]. According to 2018 report of the World Health Organization (WHO), there are 34.703 (16.5%) new lung cancer diagnoses per year in our country. Declared figures are 29.405 (24,7%) in males and 5.298 (5,8%) in females [10].

Molecular Epidemiology

According to the molecular epidemiological data from the two major genome studies carried out in the United States of America and Japan (The Cancer Genome Atlas (TCGA) study and Japan Molecular Epidemiology for lung cancer study), the rate of EGRF mutation in adenocarcinomatous cases is higher in Asian people than in caucasians. Other mutations have been found at a higher rate in caucasians. The mutation rates in caucasians and Asian people were notified as; EGFR: 14.6% and 51.1%, KRAS: 32.9% and 9.3%, TP53: 45.2% and 20.7%, BRAF:
9.6% and 1.3%, PIK3CA: 5.9% and 2.6%, KEAP1: 17.8% and 0.5%, NF1: 10.9% and 0.5%, STK11: 17.8% and 0.7%, RBM10: 8.7% and 0.1%, MET: 7.8% and 0.1%, respectively. In cases with squamous carcinoma, all mutations rates are higher in caucasians. These mutations rates for caucasians and Asian people are TP53: 81.2% and 49.1%, PIK3CA: 14.5% and 6.8%, KEAP1: 12.7% and
0.9% and NFE2L2: 15.8% ve %13,6 [11].

Etiology of Lung Cancer, Risk Factors and Prevention

Various risk factors have been identified in lots of studies on etiology of lung cancer.

Tobacco and Tobacco Products

The most important risk factor that play a part in lung cancer development is the cigarettes. It is known that approximately 50 of more than 4000 chemicals in cigarette smoke have a carcinogenic effect [12]. Organic and inorganic components such as polycyclic aromatic hydrocarbons, aramaticamins, N-Nitrosamines, benzene, vinyl chloride, arsenic and chrome are also major carcinogens present in cigarette smoke. Additionally, radioactive material such as radon and its decay products (bismuth and polonium) are also present in cigarette smoke.

The relative risk of getting cancer is 10-30 times higher in smokers than non-smokers. It was notified that the cumulative risk of getting cancer for a non-smoker for perpetuity is less than 1% and the cumulative risk of developing lung cancer for a heavy smoker is 30%. One out of every six smokers are getting lung cancer. The risk of lung cancer is linked to the

amount of cigarettes consumed daily, the age of starting smoking, the depth of inhalation, tar and nicotine content and physical properties of smoked cigarettes [13]. The main indicator used to determine the level of cigarette consumption; is the frequency of smoking. Cigarettes in current use contain less tar and nicotine; therefore, smokers increase the number and frequency of inhalations. Deep inhalation leads the peripheral epithelium to be affected by carcinogens and induces the lung adenocarcinoma development [14]. Although 80% of lung cancer occur in smokers, 20% of all smokers develop lung cancer. This variability likely stems from the environmental and other genetic factors [5]. Detrimental effect of the smoking is not limited to the harm to the smokers, people who inhale cigarette smoke have a high risk of lung cancer although they do not smoke. It has been notified that 10-15% of the cases with lung cancer in the United States of America are seen in people who had never smoked [15].

Environmental Vocational Risk Factors

Some chemicals and physical factors encountered in living and workplace environment may cause lung cancer. Among these substances, the most studied substance is asbestos. Environmental asbestos exposure in rural areas poses a significant problem in our country. Asbestos exposure can cause mesothelioma, which is a malignant tumor of the pleura, as well as lung cancer; additionally, the association of it with laryngeal cancer has also been revealed. In the studies conducted, it has been found that asbestos exposure increases the risk of lung cancer by 5.2 times, cigarette exposure increases by 10.3 times, and both together increases by 28.4 times. [16, 17].

Radon is a colorless and odorless gas that does not react chemically. People are exposed to an average annual dose of 2.8 mSV depending on their living standards, physical characteristics of the living environments, and changes in geographical and geological conditions.

Radon is low reactive and consequently it does not chemically bind to tissue when inhaled. Decay products of radon form radioactive aerosols by clinging to dust and particles, and they are carried in this way and taken through respiratory tract. Radioactive particles penetrating into the tissues of the lung cause injury to the lung. The strongest effect of radiation is that it causes mutations in DNA, which is the genetic material of the living organism [18]. Indoor and outdoor air pollution, arsenic contamination of potable water, vocationally metal exposures are also involved in the etiology of lung cancer. Another cause

of indoor air pollution is the smoke released during cooking. It has been shown in studies conducted on far eastern housewives that particularly the far eastern cuisine cooking style, that is, the way of cooking over high heat with a lidless wok is risky[5].

Especially urban air pollution that occurs in settlements where industry is intensive and traffic density is high, and indoor air pollution that occurs indoors has an influence on the lung cancer development [19]. Diesel waste has carcinogenic properties due to its benzene, formaldehyde and 1,3-butadiene content. It has been shown that, especially in transport sector, vocational diesel wastes exposure cause a 30-50% increase in the relative risk of lung cancer [20].

Familial, genetic factors

The lung cancer risk is high in people who have a history of lung cancer in their first degree family. However, there is no precise genetic transition in the development of lung cancer. The fact that people live in the same environment and have similar habits may also play a part in the high risk of cancer in members of the family [19].

Other factors

It has been revealed that lung cancer risk increases in the cases with chronic obstructive respiratory diseases, interstitial lung diseases, previous pulmonary tuberculosis α and 1antitrypsin deficiency. Besides, it has been reported that infections of chlamydia, Human Papilloma Virus (HPV), Human Immunodeficieny Virus (HIV) and tuberculosis infections predispose to lung cancer [5].

Lung cancer is more common in people with a low level of education, people in lower socioeconomic classes, and black people. However it may be discussed that high cancer incidence is associated with the prevalence of other risk factors in this group.

A diet rich in red meat, dairy products, saturated fat and lipids has been shown to increase the lung cancer risk [21]. Vegetable and fruit consumption has a protective effect on cancer due to its antioxidant effect [22]. Accordingly, those who do not consume enough vegetables and fruits may have a higher risk.

There is scientific evidence that physical activity reduces the lung cancer risk [23]. Consequently, the healthy lifestyle in which tobacco and tobacco products are not used, a healthy diet habits, active lifestyle and in which adequate cardiorespiratory capacity are provided reduces the cancer risk, particularly lung cancer risk [24].

While innumerous studies have been conducted on this subject, there is not an available effective medicine treatment in lung cancer chemoprevention at the present time [5].

The major risk factor for lung cancer development is the cigarettes and the smoking cessation is the primary prevention method from lung cancer. In countries where effective smoking cessation programme are implemented, traditional model of lung cancer has been changing and %25 of all cancer in non-smokers have lung cancer. In the future, preventive efforts and researchs will turn towards possible non-smoking risk factors as well as smoking. Healthy lifestyle recommendations such as staying at a healthy weight, feeding healthy and increasing physical activity are also vital for protecting against lung cancer as well as avoiding tobacco and tobacco products. Measures to protect public health; implementation of anti-smoking programs, prevention of environmental tobacco exposure, prevention of environmental carcinogen exposure for employee health, and taking measures to provide clean air are effective steps that should be taken to reduce the lung cancer risk. Advanced studies on the genetic characteristics of the disease and the molecular basis of carcinogenesis will be the basis of effective preventive efforts.

Screening Programmes for Lung Cancer

Survival rates are low as patients with lung cancer are generally diagnosed in advanced stages of the disease, five-year survival rates is notified as 18%. In the early stage of the disease, five-year survival rates can reach 80% with an effective treatment approach [4]. The aim of lung cancer screenings is to make the disease treatable by identifing individuals at risk for lung cancer, and to apply effective treatment approaches by detecting the disease at an early stage[25]. The only method that has been shown to be effective for lung cancer for today is annual screening via low dose computed tomography (LDCT). It was first shown in 2011 that this method reduces the mortality of lung cancer. In the multicenter national screening study "National Lung Cancer Screening Trial- NLST", conducted on 53.454 cases in the United States of America, lung cancer-related mortality has been found to be 20% lower than the control group [26]. Since narrow-scoped studies in Europe have ended up to be negative in terms of LDCT, LDCT screening has not been accepted as a screening method in Europe. In the largest European study, the Dutch-Belgian joint project NELSON, 15.822 participants were enrolled, and the volumetric analysis of the detected nodule, unlike other studies, was also evaluated. In this study, it was shown that

LDCT screening reduces mortality in males by 26% [27]. While the tendency to use it has been gradually increasing after the NELSON study, which resulted in a positive result, LDCT has not yet been implemented as a mass screening method in many countries around the world and in our country. Unclarified problems such as the uncertainty of the most appropriate risk group and method, high false positive results, difficulties in managing case with a positive screening, overdiagnosis, and radiation risk are the most important reasons why LDCT scanning is not widespread. Studies on to combine LDCT with biomarkers in order to reduce false positivity, which is the biggest problem, are ongoing and encouraging hope[28].

Histopathological subtypes of lung cancer

The definition of lung cancer includes malignancies arising from the airways and pulmonary parenchyma. Approximately 95% of lung cancers are non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). Classification of lung cancer allows us to use a common language by revealing the subtypes of the disease and the histopathological diagnostic criteria of its subtypes, which ultimately leads to better lung cancer management. The use of histopathological classification for lung cancer enables an international standard for clinicians and pathologists, while it allows them to plan treatment and watch the clinical course after treatment.

A great number of revisions have been made to the histopathological classification of lung cancer in accordance with developments in the historical process. The last update was published in 2015. Histopathological classification of lung cancer which is updated by World Health Organisation in 2015 is given in Table 1[29, 30].

The most common NSCLC subtype in our country is adenocarcinoma with 47.1%. The percentage distribution of histological subtypes of thorax cancers in line with Turkey Compositional Data Base is given in Table 2 [9].

Symptoms and Findings in Lung Cancer

Symptoms in patients with lung cancer may be symptoms such as weight loss, asthenia, which are nonspecific, depending on intrathoracic spread of the primary tumor, paraneoplastic, or depending on distant metastasis [31]. The disease may be asymptomatic in the early stages. Symptoms associated with the primary tumor are; cough, dyspnea, hemoptysis, and chest discomfort. Persistent cough and dyspnea caused by endobronchial

lesion or postobstructive pneumonia are the most common symptoms of lung malignancies. These symptoms, which can sometimes be accompanied by wheezing and stridor, are present in 60-75% of the cases. Hemoptysis may also be seen, it is rarely massive[32].

In 40% of patients, symptoms are associated with spread of the tumor or its lymphatic spread to the intrathoracic nerves, chest wall, pleura, vascular structures, and/or organs [31-33]. Recurrent laryngeal nerve paralysis is common in left-sided tumor and causes hoarseness. Right-sided recurrent laryngeal nerve paralysis is rare as the course of the nerve in the thoracic cavity is short in right side. Depending on the mediastinal involvement of the tumor, phrenic nerve paralysis may occur and ends up with hemidiaphragm elevation [31].

Superior sulcus tumors sometimes occur with all the classic findings of Pancoast's syndrome, and sometimes occur with some symptoms of it. Pancoast's syndrome: It is a clinical picture consisting of shoulder, arm and back pain, horner's syndrome (unilateral miosis, ptosis, enophthalmos and anhidrosis) and sympathetic chain in the distribution of C8-T1 nerve root depending on brachial plexus, rib and vertebra involvement, and atonia, pain and paraesthesia in the arm and hand depending on stellate ganglion involvement of the tumor [31].

Chest wall invasion can cause rib destruction or painful soft tissue mass. Pleural effusion may emerge as a paramalignant fluid by the indirect effects of the primary tumor as it may be related to the direct spread of the tumor and and dyspnea and chest pain may develop for this reason[31-33].

Lung cancer can sometimes be seen with superior vena cava syndrome characterized by edema and venous distension in the arm, neck, upper chest in a patient who complaints of difficulty in breathing, headache, blurred vision, dizziness, and delirium [32].

Lung cancer most often metastasizes to the lymph nodes, liver, adrenal glands, bone, brain, and pleura. Nervous system involvement most often occurs by intracranial metastases; however, neurological symptoms may occur in association with paraneoplastic syndromes. It has been notifed that the primary focus in 70% of patients with symptomatic brain metastases is the lung [31-33].

Diagnosis and Staging in Lung Cancer

In the approach to patients with lung cancer, as in all other cancers, staging is of

fundamental importance for planning and implementing an effective treatment approach, determining the post-therapy treatment-follow-up method to be applied, and predicting the prognosis. TNM staging is used in lung cancer. In this system, T factor defines tumor-specific characteristics including tumor size, local invasion and tumor associated nodules, N defines lymph node involvement, and M defines distant metastases. The eighth edition of lun cancer staging, which is organized by the International Association for the Study of Lung Cancer (IASLC), entered into force in January 2017. T defining characteristics are given in Table 3 and the eighth Staging System is given in Table 4 [34, 35].

The distribution of NSCLC by the stages according to the data from Turkey is given in Figure 3, 84.5% of the cases in our country are diagnosed in the locally advanced-advanced stage [9].

It is recommended to use TNM staging also in small cell lung cancer (SCLC). The definitions of 'limited' and 'common' used in clinical practice applications are not suitable especially for patients included in the clinical investigation process.
[34, 35]..

For staging in the initial evaluation of a patient with lung cancer, for today, it is recommended to use clinical staging by whole-body PET/CT (Positron Emission Tomography/computed tomography, contrast-enhanced brain MRI (magnetic resonance imagining) or CT.
[33].

An appropriate sample for the histopathological diagnosis of lung cancer is resection material. Besides, only almost 20% of the cases are suitable for primary surgery treatment, and the remaining 80% need to be diagnosed with a small biopsy sample. The small biopsy specimen is at least 1 mm^3 of tissue taken with minimal procedures for the diagnosis and staging of the disease, adequate for immunohistochemistry and molecular study [36]. Advances in genetics have been making new molecular tests a current issue, and the 'sufficient tissue' required for determining the treatment groups in stage IIIB and IV patients comes into prominence. The tissue taken should be sufficient for morphological evaluation, assessment of immunohistochemistry and genetic markers. Markers to be evaluated in the advanced stage patient group are EGFR, ALK, ROS 1, in all non-squamous lung cancer cases, and in case these markers are negative, it is recommended to check for BRAF, MET,

RET, ERB B2 (HER2), KRAS mutations [37].

Genetic evaluation is up to the clinician's discretion when squamous cell carcinoma is present. In case relapse develops in a patient with a driver mutation, it is recommended to check for T790M mutation in an EGFR mutant patient.

Appropriate method to be chosen for diagnosis is determined by the size and localization of the primary tumor, the presence of radiological findings of mediastinal invasion, and the clinically suspected cell subtype [38].

According to the guideline recommendations, if radiographic and clinical findings address small cell lung cancer (SCLC), the easiest applicable method for diagnosis should be chosen. In case the lesion in point addresses non-small cell lung cancer (NSCLC), the approach is determined in the direction of the potential stage:

1-Stage of the suspected lesion; T1a-cN0M0 (Stage I): Since the suspicion of distant metastasis is low in T1a(mi), T1aN0M0, T1bN0M0, T1cN0M0 cases, the suggested approach is surgery in cases with mediastinal lymph node involvement peripherally localized <30 mm and no suspicion of distant metastasis[39].

2- Cases with moderate risk of N2/N3 nodal involvement: As a general approach, mediastinal staging is recommended in patients with suspected N2 and N3 involvement in central tumors. Lesions needed mediastinal staging in the direction of clinical suspicion; are centrally located IA(T1aN0M0), Stage II (T2bN0M0, T3N0M0) or T1N1M0, T2N1M0 cases. In addition, small central lesion (<3cm), young age, adenocarcinoma histology are included in the moderate risk group
[40].

In the case of clinically N1 involvement or in the presence of a central tumor, the rates of false negativity are over 25%, since the suspected N activity cannot be clearly distinguished by PET or PET-CT as the probability of N1 involvement is high.
Preoperative mediastinal staging for T2 lesions is controversial; however, it has a 10-15% risk of occult metastasis, so it is applied in many centers [41].

3- Cases with high risk of N2/N3 nodal involvement: Lymph nodes with a size bigger than 1 cm on N2, N3 involvement locations, regardless of its size, if there is high metabolic activity in PET-CT or even if lymph node involvement is not considered, in T4 (>7 cm) and T3 (5-7 cm) cases N2/N3 involvement risk is high. In these cases, the initial biopsy option

should be these lymph nodes. There are two exceptions to this situation:

- Mediastinal infiltrating, conglomerate T4 lesions; the aim here is only a diagnostic biopsy. Supraclavicular or scalene lymph nodes; if there is N3 level involvement on the ipsilateral or contralateral, these lymph nodes should be preferred instead of the mediastinum for biopsy [42].

Choice of diagnostic method: Centrally located lesions

In recent years, endoscopic techniques have been the most appropiate methods for the diagnosis and staging of lung cancer. These methods, which are more effective in mortality, morbidity and cost compared to mediastinoscopy, have high diagnostic susceptibility and specificity.

Fiberoptic Bronchoscopy

If nodal staging will not affect the treatment decision and course, it is necessary to evaluate all patients with central lesions by fiberoptic bronchoscopy (FOB). The central lesion can be observed as exophytic, endobronchial, submucosal spreaded or externally flattened. In patients with suspected lung cancer, endobronchial evaluation advises on the necessity of endobronchial interventional procedure as well as tissue diagnosis. The diagnostic susceptibility of fiberoptic bronchoscopy in the evaluation of central lesions are 88%. Direct forceps biopsy from the observed endobronchial lesion has become the most commonly used method and the diagnostic susceptibility of this procedure was notified to be 74% [43].

It is recommended to take at least five biopsies in order to increase the diagnostic efficiency of bronchoscopy, to histopathologically diagnose the tumor and to obtain sufficient tissue for genotypic evaluation. It is sufficient to take two biopsies for diagnosis and genetic evaluation if a cryobiopsy is planned during the procedure [44, 45].

In the bronchoscopic approach, transbronchial fine-needle aspiration biopsy (TFNAB) can be tried if there is a lymph node pathologically scanned by screening methods in the right and left upper paratracheal and subcarinal areas. For this reason, often preferred lymph nodes by experienced bronchoscopists, are subcarinal and right paratracheal lymph nodes.
[46].

Endobronchial ultrasonography-guided transbronchial fine-needle aspiration biopsy

This method is an outstanding method in mediastinal staging compared to CT and PET. Endoscopic ultrasonography is an effective method that provides the opportunity to increase the number of lymph node stations that can be accessed by non-surgical methods for the diagnosis and staging of lung cancer. It is performed with real-time ultrasonography as in EBUS and the inferior pulmonary ligament, paraesophageal, subcarinal, left paratracheal, and sometimes aorticopulmonary lymph nodes can be sampled. The susceptibility of the method, negative predictive value, specificity and positive predictive value are notified as 89%, 91% and 100%, respectively [47].

Peripheric localized lesions

The success of diagnosis of bronchoscopy is low in lesions smaller than 2 cm and localized in the proximal zone and on two-thirds of the lung. To overcome the problems of conventional bronchoscopy in peripheral lung lesions, new techniques such as fluoroscopy-guided bronchoscopy, ultrathin bronchoscopy, radial endobronchial ultrasonography and navigational bronchoscopy or a combination of these methods have been developed.

Transthoracic needle aspiration biopsy:

Transthoracic needle aspiration biopsy (TNAB) is based on aspiration or biopsy from the target tissue, accompanied by imaging methods (frequently tomography, and in lesions adjacent to the chest wall, ultrasonography). This method is often used for the diagnosis of peripherally located lesions, when the lesion cannot be reached with FOB and EBUS. While the diagnostic of the procedure has been notified as 74-90% in various series, its diagnostic susceptibility declines in <3 cm lesions[36]. Although the diagnostic efficiency of the operation is high, its complications are bleeding and pneumothorax. Pneumothorax is notified as 10-15% and the risk is high in case of emphysema, bullous disease, and chronic respiratory failure. It is recommended to take at least two biopsies in order to increase the diagnostic efficiency of the operation, to histopathologically diagnose the tumor and to obtain sufficient tissue for genotypic evaluation [48].

Additional surgical interventions may be required for diagnosis and staging when biopsy procedures for the primary tumor are not diagnostic. These methods are cervical mediastinoscopy, video-assisted thoracoscopic surgery (VATS), anterior mediastinotomy,

video-assited mediastinal lymphadenectomy (VAMLA) and transcervical extended mediastinal lympadenectomy (TEMLA). Among these methods, VATS provides information on the chest wall and mediastinal invasion of the lesion (T), ipsilateral mediastinal lymph nodes (stations no. 4, 5, 6, 7, 8, 9, 10 and 14), evaluation of pleural nodule or effusion (M1a) [49].

Pleural involvement of lung cancer occurs in the form of pleural metastasis and effusions, a vast number of pleural and/or pleural-based nodules, and spread of the primary tumor to the pleura and chest wall. The visceral or parietal spread of the primary tumor should be differentiated from metastatic spread to the pleural cavity, as direct spread is potentially suitable for resection. Pleural involvement, in which malignant cells are shown in pleural fluid, is staged as M1a and is not suitable for the surgical approach. Therefore, in cases with suspected lung cancer, pleural fluid cytology and/or pleural biopsy is required [50].

Indications for thoracentesis is seen in patients with suspected lung cancer and pleural effusion. Thoracentesis is recommended in the form of taking 20-50 ml of pleural fluid, if possible, under ultrasonography guidance. If cytology is negative on the first examination, another sampling should be carried out before the biopsy operation. If thoracentesis is not diagnostic, biopsy is required for tissue diagnosis.
[51].

Treatment Approaches in Lung Cancers

The treatment decision in lung cancers is mainly made in the direction of specific patient related traits such as the tumor histology, stage of the disease and age, pulmonary functions and co-morbidities. Staging is the most significant step to determine treatment options and anticipate the prognosis. Non-small cell lung cancer (NSCLC) is a quite heterogeneous group of diseases. The five-year survival rate is 18% and in the NSCLC

with an anatomical resection, in the stage 1 and 2, survival rate is 60-80% [52]. Localized, stage 1 and stage 2 diseases constitute the 30% of all NSCLC.

After cardiopulmonary adequacy was evaluated in all patients planned for regional treatment, postoperative mortality and morbidity should be determined with risk-specific models Especially patients over 65 years of age may have many comorbidities about age and lifestyle. Postoperative mortality and morbidity in patients who are candidates for surgery can be anticipated by the levels of forced expiratory volume (FEV1) and carbon monoxide diffusion capacity in the pre-operative first second.

In patients with low FEV1 and DLCO results, further evaluation should be performed by an exercise test. The possibility of complications is high in patients with maximum oxygen consumption of 10 mL/kg/min. Surgical resection is acceptable if the predicted FEV1 and DLCO are greater than 40%.

Treatment in stage I and II non-small cell lung cancer:

The standard treatment approach in patients who are medically suitable for surgery, non-metastatic stage I and II with no mediastinal invasion; is surgery [52, 53].

Lobectomy is the surgical removal of a lobe and is generally accepted to be the optimal procedure for the patient with early-stage NSCLC. Video-assisted thoracoscopic surgery (VATS) in early-stage disease is an alternative method to open thoracotomy, and is also the proper approach for Stage 1 tumors [52]. The treatment approach algorithm for patients in this group is presented in Figure 4 [34]. The eighth staging system has been used in lung cancer staging since the beginning of January 2017 and tumor size, T factor has become more crucial in this new staging system [34]. In recent years, smaller nodules and approach models to these lesions have been the subject of research, especially by showing a 20% reduction in lung cancer-related mortality as a result of the "National Lung Screening Trial" study, and by constituting a national screening program in many countries [34]. The radiological pathological classification is organized according to the new staging and it has been notified how to measure in solid nodules and how to code 'T' [35]. According to this arrangement, adenocarcinoma in situ was coded as Tis if it is an adenocarcinoma smaller than 3 cm, with a growth pattern limited to alveolar structures, and without vascular, pleural, stromal growth, and was coded as T1mi

if it is minimally invasive adenocarcinoma with an invasive component less than 5 mm and smaller than 3 cm, in the areas of lepidic-pattern adenocarcinoma. T is determined by measuring the solid component in partial solid lesions; however, the whole size is recorded as ground-glass and solid components.

In view of such information, lobectomy is outstanding compared to segmentectomy and wedge resection in squamous cell carcinoma. Lobectomy is betterness in adenocarcinoma; however, it has equivalent results with segmentectomy[54, 55]. Additionally, different metastatic, survival, and recurrence features have been notifed in adenocarcinoma subgroups, including the worst micropapillary and solid adenocarcinoma. While lobectomy is still a proper approach in solid lesions radiologically greater than 2 cm, limited resections can be sufficient in minimally invasive adenocarcinoma and adenocarcinoma insitu or adenocarcinoma subgroups with a lepidic pattern that ground glass density is radiologically observed.
[56].

In the early stage patient, after the R0 resection margin is obtained, sampling/dissection from at least six lymph nodes/stations is recommended. Sampling should include stations 10, 4, 7 for right-sided lesions, and stations 5, 6, 7 for left-sided lesions [57].

Stereotactic Radiotherapy (SRT) is the proper approach for patients who are not suitable for surgery due to their comorbidities or patients who do not accept the surgical approach and are in Stage I with peripherally localized lesion. The five-year local control rates are notified as 90% by this method and acute treatment toxicity rates are very low except in patients with concomitant interstitial lung disease, fatal toxicity might develop in case of interstitial pathology [56]. SRT can be implemented by special planning methods in cases with central (2 cm close to critical organs) Stage I cases that are not suitable for surgical resection; however, it is not suitable for practices in the area named ultra-central, which might include the main bronchus and trachea[58].

There is an adjuvant chemotherapy indication in all patients with pathological Stage II who underwent resection and in patients with 4 cm and above Stage IB [58]. Concomitant comorbidities should be taken into consideration during the post-operative recovery period when adjuvant chemotherapy is planned and it should be decided by discussions in the multi-

disciplinary council. Goal-directed therapies and immunotherapies are not also implemented in adjuvant therapy practice.

Treatment of stage III non-small cell lung cancer:

Stage III disease is a quite heterogeneous group, the treatment in this group of patients has been controversial in many aspects. According to the seventh stage, stage III disease meant the spread of the tumor to extrapulmonary structures (T3 or 4) and mediastinal lymph nodes (N2 or N3). According to the eighth staging system, hilar, intrapulmonary, and peribronchial lymph node involvement (T3N1), which accompanies a tumor over 5 cm, or a tumor greater than 7 cm (T4) without lymph node involvement are included in this group. There is no difference in the definition of clinical N in both the seventh and eighth staging. T3/T4 N3 disease, which is a new definition, is defined as stage IIIC[34,35].

Approach in locally advanced disease suitable for resection:

The basic approach at this stage is resection of the primary tumor as in stage I and II disease even though mediastinal lymph node involvement is not detected in the pathological staging if it is anticipated that R0 resection can be performed[56]. Pathological staging of the mediastinum should be definitely performed if the patient has N2 and it is considered that patient have a single-station involvement suitable for the operation. Cranial magnetic resonance imaging (MRI) should be in all of these patients[56, 60].

In an international randomized, controlled trial, N2 patients suitable for resection were randomized to the surgical and curative C-RT arms after induction CRT, and there was no difference in total survival between the two groups. In this study, the survival rate without progression of the operation was higher in the patient group without right pneumonectomy compared to the surgery group[61]. According to the opinions of international guides on this subject [56, 60] :

- If intraoperative N2 disease is detected despite all detailed staging evaluations, surgical resection should be completed and chemotherapy should be subsequently performed (I, A).
- If a single station is detected to be N2 in the pre-operative pathological nodal evaluation, adjuvant chemotherapy after resection, surgery after induction CT, and surgery after induction C-RT are proper choices. Post-operative RT is not a standard

treatment; however, it can be an alternative after a detailed evaluation of the risk possibility of local and regional relapse (IV, C).

- In cT4N0 cases, nodal staging should be performed by invasive methods, adjuvant CT should be implemented after resection if R0 resection can be obtained.
- After induction CT+/-RT is given to be regressed the stage for N2 which was detected before the operation, pneumonectomy should be avoided.

Locally advanced disease unsuitable for resection:

Locally advanced non-small cell disease unsuitable for resection comprises cases that which it was initially decided by a multidisciplinary team that R0 resection cannot be performed after induction chemotherapy or diagnostic procedures.

The proper treatment in this patient group is chemo-radiotherapy. Treatment can be planned concurrent or sequentially. Sequential therapy is a treatment that lasts 6-7 weeks that 60-66 Gy doses are given in 30-33 fractions after induction chemotherapy. The recommended proper treatment approach is concomitant C-RT as survival rates are higher in patients with the suitable general condition and pulmonary functions. Sequential C-RT is recommended in elderly patients and patients with comorbidities.

Guideline recommendations in locally advanced patients unsuitable for resection [53, 56]:

- The proper treatment approach in stage IIIA and IIIB patients not suitable for resection is concurrent C-RT Sequential C-RT is recommended if concurrent therapy is not suitable due to age and/or comorbidities (I, A).
- Prophylactic cranial RT is not seen in this group of patients (II, A).
- The proper chemotherapy option in the treatment is combinations with cisplatin, if there is no contraindication for not using it, there is no evidence for the use of carboplatin as a stand-alone radiostimulant (I, A).
- In the literature, platinum-containing protocols are recommended as chemotherapy if contraindications are out (I, A)

Immune checkpoint inhibitor therapy (ICIT); Durvalumab therapy is suggested in patients not progress after CRT with locally advanced disease, in some guidelines, this therapy is recommended for patients if they have more than 1% Programmed cell death receptor-related ligand (PD-L1)[53, 62].

Treatment in anvanced stage lung cancer:

The treatment goal in stage IV NSCLC is to prolong life by keeping the treatment-related side effects at a minimum level without impairing the quality of life. The key features that guide the treatment and determine the prognosis in these patients are as follows[53, 63].:

- The prevalence of the disease, the number and region of metastasis, and the presence of a metastasis-related symptom,
- Metabolic activity of the tumor, determined by Positron Emission Tomography (PET) [64].
- Squamous and non-squamous histology,
- The presence of driver mutation in cases with adenocarcinoma, and the presence of Epidermal growth factor receptor (EGFR), Anaplastic lymphoma kinase (ALK), and ROS1
- The other rare driver mutations: BRAF V600, Human Epidermal Growth Factor Receptor (HER2), Neurotrophic Receptor Tyrosine Kinase (NTRK), MET, and RET
- Expression of highly programmed cell death receptor-related ligand (PD-L 1) in the tumor.

Patient without driver mutation: In this group of patients, if PD L-1 is expressed at a low or moderate level, it has been shown that the combination chemotherapy (biological agent may be together with bevacizumab) is more proper than the best supportive treatment[63].

Revealing the molecular pathways and driver mutations in patients with lung cancer made a breakthrough in the treatment and a distinct prolongation has been seen in the survival rate without progression compared to chemotherapy by using goal-directed therapies at the first stage.

Approach in the patient with oligometastatic:

PET CT, invasive mediastinal staging, cranial MRI examination should be performed to plan curative treatment in patients with a primary tumor potentially suitable for surgery and detected nodular lesions in the ipsilateral (T3-T4) or contralateral lung (M1a). The proper treatment method in patients suitable for resection is the resection. Each tumor is separately staged in the presence of multiple primary lung cancer[65, 66].

If there is a lymph nodule at the N0,1 level, and if the primary lesion is suitable for resection in a patient with isolated brain metastasis, whole-brain radiotherapy is the proper approach after curative treatment of both lesions[66]. Similarly, in case primary lung lesions suitable for resection, N0, 1 lymph node involvement, and isolated adrenal metastasis at the clinical staging, systemic chemotherapy is the proper approach after curative treatment of both lesions after invasive mediastinal staging[65]. After curative treatment, the curative approach to these lesions is recommended after systematic staging also in the case of isolated bone metastasis, adrenale, and brain at metachronous feature. [53, 66].

Treatment Approaches in Small Cell Lung Cancer

Approximately 20% of all lung cancers are neuroendocrine carcinomas, 14% of these are small cell lung cancer (SCLC)[67]. Small cell lung cancer has the traits of rapid doubling time, high growth fraction, and the ability to metastasize at an early period, and hematogenous metastasis is seen in 2/3 of the cases during diagnosis.

A surgical approach is possible only in Stage I patients who are 2-5% of cases. Mediastinal staging with EBUS and/or EUS is needed in this patients group. Pathological staging is not required to specify treatment approach in patients apart from this[67].

A detailed staging in all patients with small cell lung cancer will be the treatment guide for radiation therapy. For this purpose, thoracic, abdomen CT and cranial MRI should be planned in patients. In the presence of anemia, thrombocytopenia, and neutropenia, bone marrow aspiration should be planned, it is not required except in these cases. It should be decided that limited disease by PET-CT. The limited disease is a lesion that is limited to the hemithorax and can get into the safe RT area. The common disease refers to a disease that overflows the hemithorax that also includes malignant pleural and pericardial effusion. While contralateral mediastinal and ipsilateral supraclavicular lymph nodes are within the scope of limited diseases, contralateral hilar and supraclavicular LN are within the scope of common diseases. Stages I – III are suitable for curative RT according to staging; however, T3 and T4 lesions caused by multiple nodules are in the scope of common diseases[68].

The treatment goal is curative in the presence of limited disease to the thorax and platinum-based chemotherapy (cisplatin+etoposide) together with accelerated hyper-fractionated radiotherapy is the proper approach. The treatment goal for the common disease

is palliative. In limited disease to the thorax, prophylactic cranial irradiation is recommended in case of partial or total response. The efficiency of consolidative radiotherapy has been proven in cases that had a complete or almost total response to systemic chemotherapy in patients with common disease[68].

Palliative treatment, which starts with the first professional communication in all patients diagnosed with lung cancer, is the most significant component of the approach to these patients.

RESOURCES

1. Global cancer observatory (GCO). Cancer Today. Cancer Fact Sheet. Access Date: April 25, 2020 Available from: http://gco.iarc.fr/today/data/factsheets/cancers/15-Lung- fact-sheet.pdf.
2. Torre LA, Siegel RL, Jemal A. Lung cancer statis- tics. Adv Exp Med Biol 2016; 893:1–19.
3. Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68(6): 394–424.
4. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. CA Cancer J Clin 2020; 70: 7-30.
5. Bade BC, Dela Cruz CS. Lung Cancer 2020: Epidemiology, Etiology, and Prevention. Clin Chest Med. 2020 Mar;41(1):1-24.
6. Torre LA, Bray F, Siegel RL, et al. Global cancer sta- tistics, 2012. CA Cancer J Clin 2015;65(2):87–108.
7. American Lung Association. Trends in tobacco use. 2011. Available at: https://www.lung.org/assets/ documents/research/tobacco-trend-report.pdf. Access Date: April 25, 2020
8. Jeon J, Holford TR, Levy DT, et al. Smoking and lung cancer mortality in the United States from 2015 to 2065: a comparative modeling approach. Ann Intern Med 2018;169(10):684–93.
9. Turkey Cancer Statistics, 2016, T.R. Ministry of Health, Turkey Public Health Agency, Ankara, 2019.
10. Global cancer observatory (GCO). Cancer Today. Turkey Fact Sheet. Access Date: April 30, 2020 Available from: http://gco.iarc.fr/today/data/factsheets/populations/792- turkey-fact-sheets.pdf.
11. Izumi M, Suzumura T, Ogawa K, et al. Japan Differences in molecular epidemiology of lung cancer among ethnicities (Asian vs. Caucasian).J Thorac Dis 2019;

http://dx.doi.org/10.21037/jtd.2019.08.61.

12. Smith CJ, Perfetti TA, Mullens MA, et al. "IARC group 2B Carcinogens" reported in cigarette main- stream smoke. Food Chem Toxicol 2000;38(9): 825–48.
13. Harris JE, Thun MJ, Mondul AM, et al. Cigarette tar yields in relation to mortality from lung cancer in the cancer prevention study II prospective cohort, 1982-8. BMJ 2004;328(7431):72.
14. Wynder EL, Hoffmann D. Smoking and lung cancer: scientific challenges and opportunities. Cancer Res 1994;54(20):5284–95.
15. Pelosof L, Ahn C, Gao A, et.al. Proportion of Never-Smoker Non–Small Cell Lung Cancer Patients at Three Diverse Institutions, J Nat Cancer Inst. 2017; 109: djb295
16. Metintaş M. Turkish Mesothelioma Working Group Public Health Institute of Turkey Eskişehir Osmangazi University. Turkey Asbestos Control Strategic Plan Final Report. Turk Thorac J 2015; 16(Suppl 2); S1-S26.
17. Markowitz SB, Levin SB, Miller A et al. Asbestos, Asbestosis, Smoking and Lung Cancer. Am J Respir Crit Care Med 2013; 188(1): 90-96.
18. Darby S, Hill D, Auvinen A, et al. Radon in homes and risk of lung cancer: collaborative analysis of individual data from 13 European case-control studies. BMJ 2005; 330:223.
19. Bilir N. Epidemiology of Lung Cancer. In: Mirici A, Babaoğlu E, Mutlu P, editor. Chest Diseases.1. Edition. Ankara TÜSAD Educational Books Series, 2019, ISBN: 978- 605-89519-4-5.
20. Lipsett M, Campleman S. Occupational exposure to diesel exhaust and lung cancer: a meta-analysis. Am J Public Health 1999;89(7):1009–17.
21. Gnagnarella P, Caini S, Maisonneuve P, et al. Carcinogenicity of high consumption of meat and lung cancer risk among non-smokers: a comprehensive meta-analysis. Nutr Cancer 2018;70(1):1–13.
22. Vieira AR, Abar L, Vingeliene S, et al. Fruits, vegetables and lung cancer risk: a systematic review and meta-analysis. Ann Oncol 2016;27(1):81–96.
23. Pletnikoff PP, Tuomainen TP, Laukkanen JA, et al. Cardiorespiratory fitness and lung cancer risk: a prospective population-based cohort study. J Sci Med Sport 2016;19(2):98–102.
24. Laukkanen JA, Pukkala E, Rauramaa R, et al. Cardiorespiratory fitness, lifestyle factors and can- cer risk and mortality in Finnish men. Eur J Cancer 2010;46(2):355–63.
25. Thomas NA, Tanner NT. Clin Chest Med 2020; 41: 87–97.
26. The National Lung Screening Trial Research Team. Reduced Lung-Cancer Mortality with Low-Dose Computed Tomographic Screening. N Engl J Med 2011; 365:395-409.
27. de Koning DB, Van Der Aalst C, de Jong PA, et al. Reduced Lung Cancer Mortality with Volume CT Screening in a Randomised Trial. N Engl J Med 2020; 382: 503-513.

28. Benzaquen J, Boutros J, Marquette C, et al. Lung Cancer Screening, towards a Multidimensional Approach: Why and How? Cancers 2019, 11, 212; doi:10.3390.).
29. Travis WD, Brambilla E, Burke AP, Marx A, Nicholson AG. WHO Classification of Tumours of the Lung, Pleura, Thymus and Heart. Lyon: International Agency for Research on Cancer, 2015.
30. Demirağ F. Pathology of Lung Cancer. In: Mirici A, Babaoğlu E, Mutlu P, editor. Chest Diseases.1. Edition. Ankara TÜSAD Educational Books Series, 2019, ISBN: 978- 605-89519-4.
31. Ost DE, Yeung SD, Tanoue LT, Gould K. Clinical and Organizational Factors in the Initial Evaluation of Patients With Lung Cancer Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2013;143(5 Suppl): e121S-141S.
32. Pastis N, Bonifazi M, Gasparini S, Silvestri G. Diagnostic workup for suspected lung cancer confined to the chest. In: Pass HI, Ball D, Scagliotti GV., editors. Thoracic Oncology. Colorado: IASLC; 2014.p.335-344.
33. Beckles M, Spiro S, Colice G et al.Initial evaluation of the patients with lung cancer: symptoms, signs, laboratory tests, and paraneoplastic syndromes. Chest 2003; 123(1 Suppl: 97S-104S.
34. Turna A, Ak G, Kömürcüoğlu BE, Yurt S, Yılmaz Ü. The eighth staging system of non-small cell lung cancer and its practical implications. Turkish Journal of Thoracic and Cardiovascular Surgery 2017;25(3):484-498.
35. Goldstraw P, Chansky K, Crowley J, Rami-Porta R, Asamura H, Eberhardt WE, et al. The IASLC Lung Cancer Staging Project: Proposals for Revision of the TNM Stage Groupings in the Forthcoming (Eighth) Edition of the TNM Classification for Lung Cancer. J Thorac Oncol 2016; 11:39-51.
36. Lung cancer: diagnosis and management. Nice Guideline. 2019 https://www.nice.org.uk/guidance/ng122 Date accessed: May 3, 2020.
37. Lindeman NI, Cagle PT, Aisner DL, et al. Updated Molecular Testing Guideline for the Selection of Lung Cancer Patients for Treatment With Targeted Tyrosine Kinase Inhibitors: Guideline From the College of American Pathologists, the International Association for the Study of Lung Cancer, and the Association for Molecular Pathology. Arch Pathol Lab Med. 2018 Mar;142(3):321-346.
38. Rivera P, Mehta A, Wahidi MM. Establishing the diagnosis of lung cancer. Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2013;143(5 Suppl):e142S-165S.

39. Schmidt-Hansen M, Baldwin DR, Hasler E, et al. PET-CT for assessing mediastinal lymph node involvement in patients with suspected resectable non-small cell lung cancer. Cochrane Database Syst Rev. 2014;11.
40. O'Connell OJ, Almeida FA, Simoff MJ, et al. A Prediction Model to Help with the Assessment of Adenopathy in Lung Cancer (HAL). Am J Respir Crit Care Med. 2016; 195(12): 1651-60.
41. Cerfolio RJ, Bryant AS, Ojha B, Eloubeidi M. Improving the inaccuracies of clinical staging of patients with NSCLC: a prospective trial. Ann Thorac Surg. 2005 Oct;80(4):1207-13.
42. Rivera P, Mehta A, Wahidi MM. Establishing the diagnosis of lung cancer. Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2013;143(5 Suppl): e142S-165S.
43. Rivera P, Mehta A, Wahidi MM. Establishing the diagnosis of lung cancer. Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2013;143(5 Suppl): e142S-165S.
44. Dietel M, Bubendorf L, Dingemans AC, et al Diagnostic procedures for non-small-cell lung cancer (NSCLC): recommendations of the European Expert Group. Thorax 2016; 71:177–184. doi:10.1136/thoraxjnl-2014-206677
45. Van der Heijden E.H.F.M, Casal RF, Trisolini R, et al. Guideline for the Acquisition and Preparation of Conventional and Endobronchial Ultrasound-Guided Transbronchial Needle Aspiration Specimens for the Diagnosis and Molecular Testing of Patients with Known or Suspected Lung Cancer. Respiration 2014; 88:500-17.
46. Adams K, Shah PL, Edmonds L, Lim E. Test performance of endobronchial ultrasound and transbronchial needle aspiration biopsy for mediastinal staging in patients with lung cancer: systemic review and meta-analysis. Thorax 2009;60(11):949-955.
47. Yasufuku K, Nakajima T, Motoori K, et al. Comparison of endobronchial ultrasound, positron emission tomography and CT for lymph node staging of lung cancer. Chest 2016;130(3):710-18.
48. Dietel M, Bubendorf L, Dingemans AC, et al Diagnostic procedures for non-small-cell lung cancer (NSCLC): recommendations of the European Expert Group. Thorax 2016; 71:177–184.
49. Silvestri GA, Gonzalez AV, Jantz MA, Margolis ML, Gould MK, Tanoue LT, et al. Methods for staging non-small cell lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2013;143(5 Suppl): e211S-250S.
50. Rivera P, Mehta A, Wahidi MM. Establishing the diagnosis of lung cancer. Diagnosis and

management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2013;143(5 Suppl): e142S-165S.

51. Metintaş M. Invasive operations in diagnosis. In: Metintaş M Guideline for diagnosis and treatment for pleural diseases for Chest diseases experts TTD, TÜSAD Edition Ankara, Bilimsel Tıp Publisher; 2016: 10-12.
52. Howington JA, Blum MG, Chang AC, et al. Treatment of stage I and II non-small cell lung cancer. Chest 2013;143(5) (Suppl):378-313.
53. National Comprehensive Cancer Network guidelines. Nonsmall cell lung cancer Version 3.2020 https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf Date accessed: May 8, 2020)
54. Veluswamy RR, Ezer N, Mhango G et al. Limited resection versus lobec- tomy for older patients with early stage lung cancer: impact of histology. J Clin Oncol 2015; 33: 3447–3453
55. Koike T, Kitahara A, Sato S et al. Lobectomy versus segmentectomy in radiologically pure solid small-sized non-small cell lung cancer. Ann Thorac Surg 2016; 101: 1354–1360
56. Postmus PE, Oudkerk M, Senan S, et al. Early and locally advanced non-small-cell lung cancer) NSCLC) ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Annals of Oncology 2017; 28 (Suppl 4): iv1–iv21
57. Darling GE, Allen MS, Decker PA, et al. Randomized trial of mediastinal lymph node sampling versus complete lymphadenectomy during pulmonary resection in the patient with N0 or N1 (less than hilar) non-small cell carcinoma: results of the American College of Surgery Oncology Group Z0030 Trial. J Thorac Cardiovasc Surg 2011; 141:662.
58. Louie AV, Palma DA Dahele M et al. Management of early-stage non- small cell lung cancer using stereotactic ablative radiotherapy: contro- versies, insights, and changing horizons. Radiother Oncol 2015; 114: 138–147.
59. Heineman DJ, Daniels JM and Schreurs WH Clinical staging of NSCLC: current evidence and implications for adjuvant chemotherapy Ther Adv Med Oncol 2017, Vol. 9(9) 599–609.
60. Ramnath N, Dilling TJ, Harris LJ, et al. Treatment of Stage III Non-small cell Lundg cancer. Chest 2013;143(5) (Suppl):314-340.
61. Albain KS, Swann RS, Rusch VW et al. Radiotherapy plus chemotherapy with or without surgical resection for stage III non-small-cell lung cancer: a phase III randomised controlled

trial. Lancet 2009; 374: 379–386.

62. eUpdate – Early and Locally Advanced Non-Small-Cell Lung Cancer (NSCLC) Treatment Recommendations https://www.esmo.org/guidelines/lung-and-chest-tumours/early-stage-and-locally-advanced-non-metastatic-non-small-cell-lung-cancer/eupdate-early-and-locally-advanced-non-small-cell-lung-cancer-nsclc-treatment-recommendations
Access Date: May 9, 2020

63. D. Planchard, S. Popat, K. Kerr, et al. CLINICAL PRACTICE GUIDELINES Metastatic non-small cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up† Originally published in 2018 – Ann Oncol (2018) 29 (suppl 4): iv192–iv237. Updated version published 18 September 2019 by the ESMO Guidelines Committee. Download the current version from esmo.org (PDF)

64. Paesmans M, Garcia C, Wong Cy, et al. Primary tumour standardised uptake value is prognostic in nonsmall cell lung cancer: a multivariate pooled analysis of individual data Eur Respir J 2015; 46: 1751-61.

65. Detterbeck FC, Franklin WA, Nicholson AG, et al. The IASLC Lung Cancer Staging Project: Background Data and Proposed Criteria to Distinguish Separate Primary Lung Cancers from Metastatic Foci in Patients with Two Lung Tumors in the Forthcoming Eighth Edition of the TNM Classification for Lung Cancer. J Thorac Oncol 2016; 11:651-65.

66. Kozower BD, Larner JM, Detterbeck FC, et al Special treatment issues in Non-small cell lung cancer. Chest 2013; 143: e369S-399S.

67. Jett JR, Schild SE, Kesler KA, Kalemkerian GP. Treatment of small cell lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2013;143: e400S-419S

68. National Comprehensive Cancer Network guidelines. Small cell lung cancer Version 3.2020 https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf Date accessed: May 9, 2020

Table 1. Histopathological Subtypes of Lung Carcinoma According to the 2015 classification of the World Health Organisation [6]

Adenocarcinoma	**Squamous cell carcinoma**	**Neuroendocrine tumors**	**The other carcinomas**
A. Preinvasive lesions Atypical adenomatous hyperplasia Adenocarcinoma in situ **B.** Minimally invasive adenocarcinoma (Tumors with the predominant lepidic pattern that its invasion less than 5 mm) **C.** Invasive adenocarcinoma Tumors with the predominant lepidic pattern that its invasion more than 5 mm Acinar-predominant type Papillary-dominant type Micropapillary-predominant type Solid-predominant type (secretes mucins) **D.** Invasive adenocarcinoma variants Invasive mucinous adenocarcinoma Colloid Low and high -grade fetal adenocarcinoma Enteric	**A.** Preinvasive lesions Squamous carcinoma in situ **B.** Squamous cell carcinoma Keratinized Nonkeratinized Basaloid	**A.** Preinvasive lesions Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia **B.**Small cell carcinoma **C**.Large cell neuroendocrine carcinoma **D.**Carcinoid tumor	**A**.Large cell carcinoma **B.** Adenosquamous carcinoma **C.** Sarcomatoid carcinoma Pleomorphic giant and spindle cell carcinoma Carcinosarcoma Pulmonary blastoma **D.** Unclassifiable carcinomas Lymphoepithelioma-like carcinoma NUT carcinoma **E.** Carcinomas originated from salivary gland Mucoepidermoid carcinoma Adenoid cystic carcinoma Epithelial-myoepithelial carcinoma

Table 2. Percentage Distribution of Histological Subtypes of Thorax Cancers [9]

Histological Type (n=11922)		**Percentage**	
LUNG (C34-C35)	**97.5**		
Non-Small Cell		**79.3**	
Squamous-Cell			37.7
Adenocarcinoma			47.1
Large-Cell			1,6
NOS			13.6
Small-Cell		**16.3**	
Other*		**4.3**	
MESOTHELIOMA (C46)	**2.6**		
Total	100.0	100.0	100.0

*Basal cell carcinoma, sarcomatoid carcinoma, spindle cell carcinoma, Melanoma, Mucoepidermoid carcinoma, sarcoma, peripheral neuroectodermal tumor

Table 3. "T" Definitions according to the eighth edition of Tumor, Node, and Metastases Staging System (35)

T (Primary tumor)

Tx: Primary tumor cannot be detected or

Tumor proven by the presence of malignant cells in phlegm or bronchial lavage, but not detected by imaging techniques or bronchoscopy

T0 No primary tumor finding

Tis Carcinoma *in situ*

T1 : A tumor with a maximum diameter of ≤3 cm, surrounded by lung or visceral pleura no invasion finding located bronchoscopically in the more proximal zone than the lobe bronchus (for instance: not in the main bronchus)

T1ami minimally invasive (mi) adenocarcinoma T1a Tumor with a maximum diameter of ≤1 cm

T1b Tumor with a maximum diameter of >1 cm but ≤2 cm
T1c Tumor with a maximum diameter of >2 cm but ≤3 cm

T2: T2 >3 cm but ≤5 cm or

Tumor with at least one of the following features

- There is main bronchus involvement without carina involvement, regardless of the distance from the carina

- There is visceral pleural invasion

- Atelectasis spreading to the hilar region or obstructive pneumonia-causing, involving part or all of the lung

T2a Tumor with a maximum diameter of >3 cm

but ≤4 cm T2b Tumor with a maximum diameter

of >4 cm but ≤5 cm

T3: Tumor with a maximum diameter of >5 cm but ≤7 cm or tumor directly invading any of the chest wall (including superior sulcus tumors), phrenic nerve, parietal pleura or

Tumor with separate nodule(s) in the same lobe

T4: T4>7 cm tumor or

Tumor invading any of the structures such as diaphragm, mediastinum, heart, major vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, carina, or tumor with separate tumor nodule(s) in different lobes on the same side

Table 4: Lung Cancer Eighth TNM Staging System (35)

	T	**N**	**M**
Occult carcinoma	Tx	N0	M0
0	Tis	N0	M0
IA1	T1a(mi)	N0	M0
	T1a	N0	M0
IA2	T1b	N0	M0
IA3	T1c	N0	M0
IB	T2a	N0	M0
IIA	T2b	N0	M0
IIB	T1a	N1	MO
	T1b	N1	M0
	T1c	N1	M0
	T2a	N1	M0
	T2b	N1	M0
	T3	M0	M0
IIIA	T1a	N2	M0
	T1b	N2	M0
	T1c	N2	M0
	T2a	N2	M0
	T2b	N2	M0
	T3	N1	M0

	T4	N0	M0
	T4	N1	M0
IIIB	T1a	N3	M0
	T1b	N3	M0
	T1c	N3	M0
	T2a	N3	M0
	T2b	N3	M0
	T3	N2	M0
	T4	N2	M0
IIIC	T3	N3	M0
	T4	N3	M0
IVA	Any T	Any N	M1a
	Any T	Any N	M1b
IVB	Any T	Any N	M1c

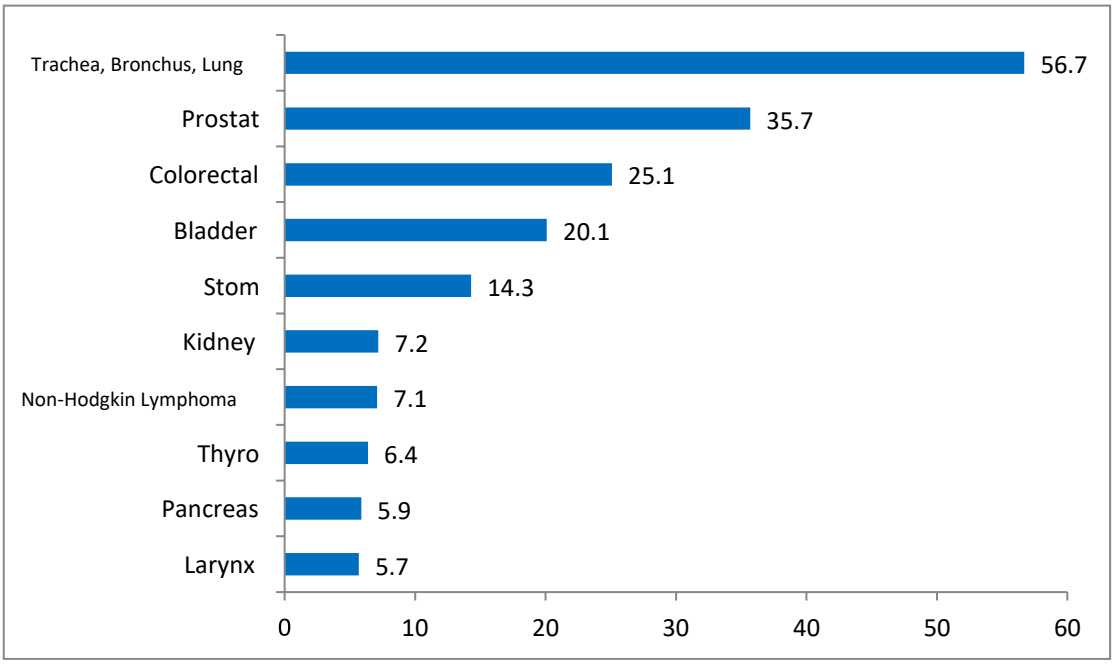


Figure 1: Age-Standardized Rates of 10 Cancer Types Which Are Most Common in Males (Turkey Compositional database, 2017) (World Standard Population, per 100,000 individuals)

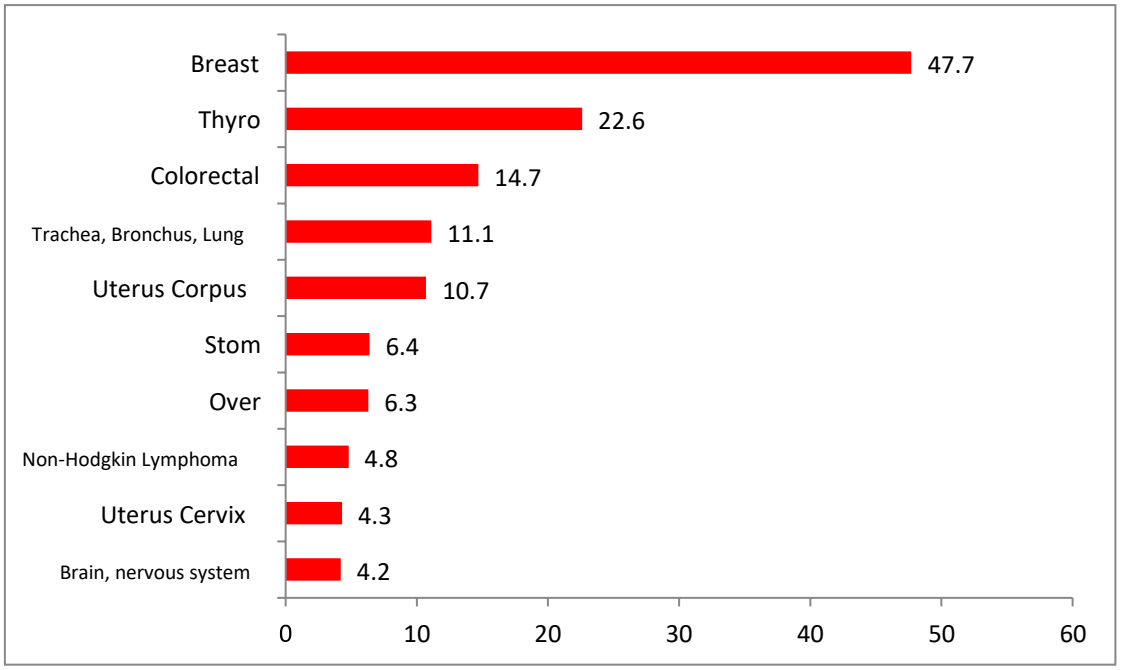


Figure 2: Age-Standardized Rates of 10 Cancer Types which are Most Common in females (Turkey Compositional database, 2017) (World Standard Population, per 100,000 individuals)

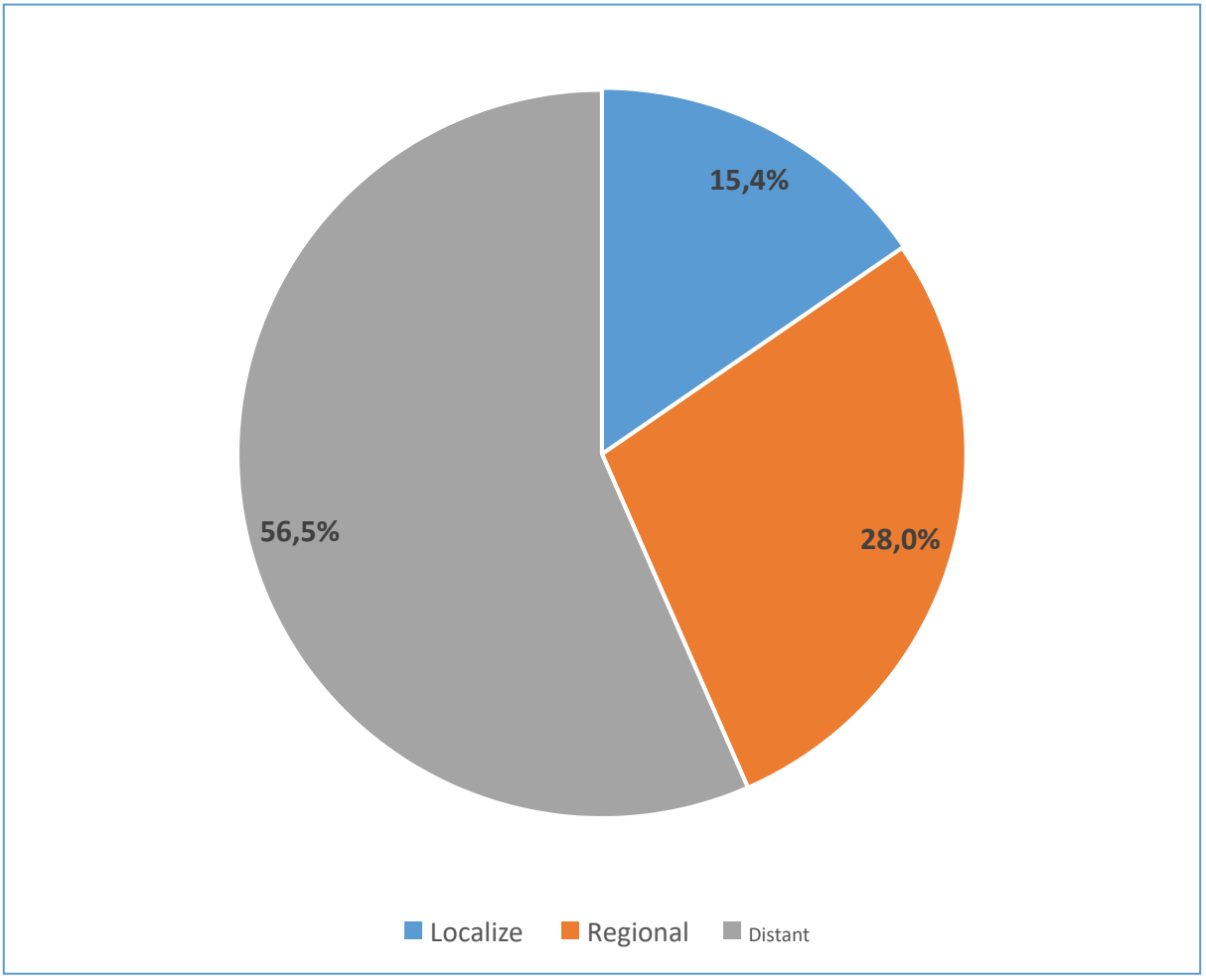


Figure 3: Percentage Distribution of Lung Cancer Stages (Turkey Compositional Data Base, 2017) [9].

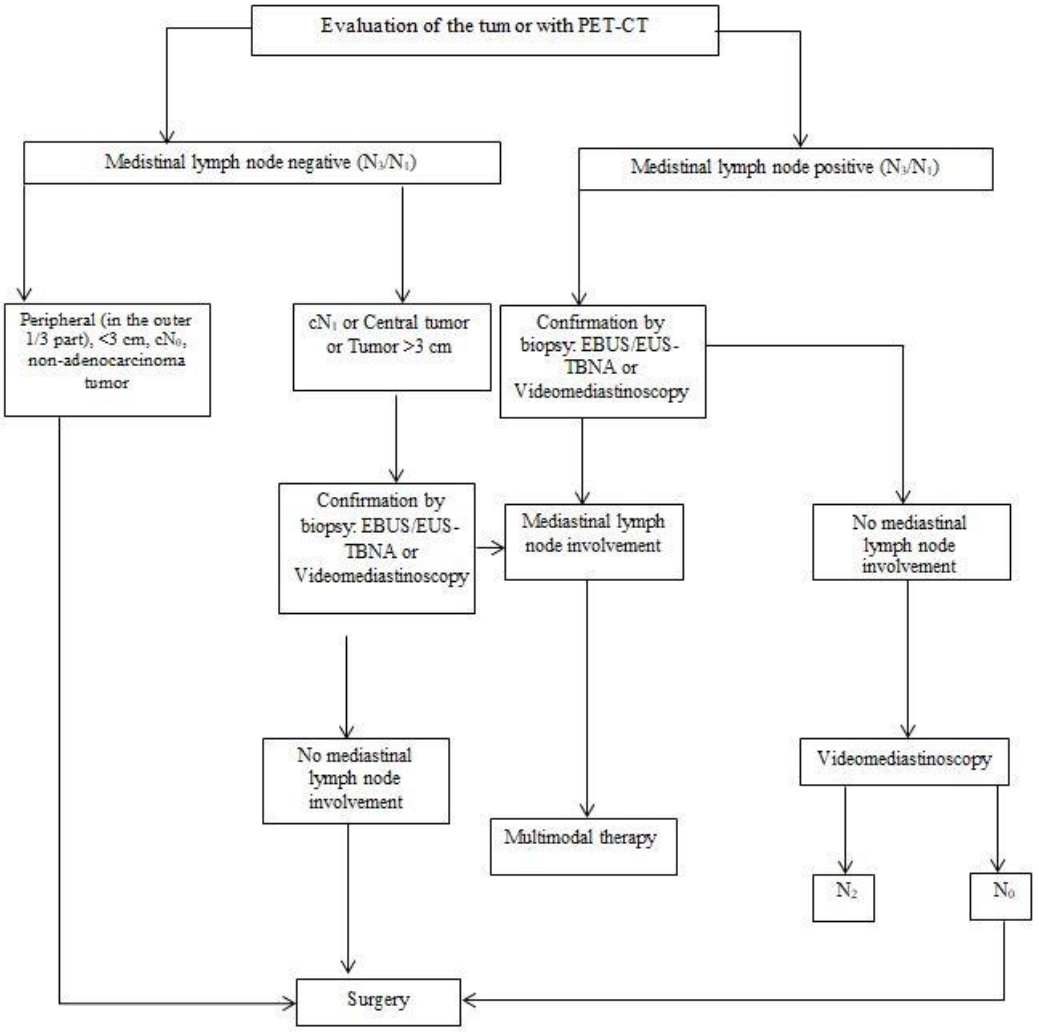


Figure 4: Evaluation of Regional Lymph Nodes İn Non-Metastatic Evaluation of Glads (34)

2.2. Breast Cancer (See Section 4)

2.3. Prostate Cancer

Epidemiology

Prostate cancer is the second most common type of cancer in males and the cause of 3.8% of cancer-related deaths [1]. It is notified that total of 1,276,106 new cases and 358,989 deaths worldwide in 2018 [1]. The incidence of prostate cancer varies across countries and is seen more in developed countries [2]. Despite the reason for this difference among countries is not known clearly, it is estimated that it arises from the frequency of prostate-specific antigen (PSA) testing [2]. In recent years, a decline in the incidence has been observed in parallel with the less implementation of PSA screening in many countries [3]. Prostate cancer stands in second place among the top ten cancer types in males in our country and its incidence is 35 per hundred thousand [4]. Prostate cancer incidence increases when the age increases [2]. While the incidence is approximately 0.3% in people younger than 50 years of age, it increases to 60% in people over 65 years of age [2, 5].

Mortality of the disease also varies across countries [2]. Even though the highest mortality has been notified in the USA with 10.7 per hundred thousand, prostate cancer-related deaths have prominently diminished in developed countries in recent years [2]. This circumstance has been linked to early diagnosis and accessibility to improved treatments [6]. Mortality increases prominently when the age increases[2]. Approximately 55% of people who die from prostate cancer are people older than 65 years of age [2]. The majority of patients are diagnosed when the disease is limited to the prostate. Survival in patients with prostate cancer varies according to disease stage. The five-year survival is approximately 100% at the early stage and it declines to 31% at advanced stage [7]. The five-year survival for patients with prostate cancer has been notified as 98% in the USA, and as 83% in Europe [8, 9].

Etiology and Risk Factors

Despite a great number of studies have been carried out on the etiology of prostate cancer, data on risk factors are less compared with other cancers. The most significant known risk factors for prostate cancer are age, ethnic origin, genetic factors, and family history [2]. Obesity, sedentary lifestyle, consumption of saturated adipose and red meat, inflammation,

infection, hyperglycemia, and environmental factors (carcinogens or radiation exposure) are the other risk factors [2, 10].

Age

Prostate cancer is the most common cancer type in elderly people [1]. In general, PSA diagnosis has increased in old people because of an increase in life expectancy and PSA screening [2]. The risk of prostate cancer starts to increase, especially from 50 years of age upward [11].

Cancer limited to the prostate has been frequently encountered in autopsies performed on patients without a prostate cancer diagnosis and who have died for another reason [12]. In performed autopsy series, prostate cancer is detected in 30% of males in the age range 60-69 and
67% of males at age range 80-89 [12].

Ethnic Difference

The prevalence of prostate cancer varies among races. While the lowest incidence is observed in citizens of Asia origin in the United States of America (USA), the highest incidence is observed in Afro-Americans [8]. In addition to the high incidence rates, prostate cancer is observed at early ages in Afro-American men. In a multicenter study with more than 12,000 cases, 8.3 percent of blacks and 3.3 percent of whites who are under the age of 50 are diagnosed with prostate cancer [13]. Many studies have asserted that genetic predisposition might enter into this difference among races [14]. It is estimated that the risk is high since Afro-American men have more common chromosome 8q24 variants which have been shown to be related to increased prostate risk [1].

Family History And Genetic Factors

Several studies have shown that hereditable genetic disorders are related to the increased prostate cancer risk and they have a part in approximately 5% of disease risks [2]. Men with a family history of prostate cancer -especially those who have immediate relatives who diagnosed at under the age of 65 years- are at high risk group for prostate cancer[15].

BRCA2, ATM, PALB2 mutations which are rarely detected are significant genetic mutations that increase the prostate cancer risk and might be a treatment target [16]. More common variants, generally single nucleotide polymorphisms(*SNP*s) can be identified in

regulatory or protein-coding regions of a gene or intra- or intergenic regions of DNA [17]. *SNP*s are relatively common, allele frequencies are found in 1 to 5 percent of the population; however, they cause slight increases in individual risk [17].

It is believed that the X chromosome plays a part in the heritage of prostate cancer since it involves the androgen receptor (AR) and is registered in the sporadic and hereditary prostate cancer forms small deletions in the Xq26.3-q27.3 region

Diet and Obesity

The relationship between western-life style and cancer in immigrants from developing countries to developed countries has been investigated and it has been observed that incidence of prostate cancer in this group has increased [18]. A study has shown that prostate cancer incidence has increased 16 times in Chinese people living in the USA compared to Chinese people living in China [19]. This circumstance shows the importance of environmental factors in terms of cancer risk.

Studies have shown that there is a positive relationship between the development of prostate cancer and the consumption of high-calorie saturated adipose [20]. It is considered that the increased reactive oxygen derivatives (ROS) based on saturated adipose consumption increase the risk of cancer [2].

One of the reasons is the overconsumption of red meat that increase the prostate cancer risk [2, 21]. A study has shown that prostate cancer risk is of higher risk in males who consume five or more servings of processed meat per week compared to males who consume one or fewer servings per week [22].

Dairy products have often been associated with an high prostate cancer risk [2]. It has been found that

calcium intake of more than 2,000 mg per day is related to prostate cancer risk [2].

In Asia, where prostate cancer incidence is low, soy and green tea, which are part of the diet, are considered to potentially prevent prostate cancer [2]. There are data that tomatoes reduce the prostate cancer risk [23, 24]. Lycopene is found in tomatoes at a high level which has powerful antioxidant characteristics [24]. Lycopene also affects androgen receptors and reverses the effects of dihydrotestosterone and also inhibits insulin-like growth factor (IGF-I)-stimulation [24].

It has been shown that vitamin D deficiency is one of the reasons that increase prostate cancer risk [2]. It is considered that the higher prostate cancer incidence in sunny countries compared to less sunny countries is the indirect indicator of this [2]. In studies conducted in line with the hypothesis that vitamin E may reduce the cancer risk due to its antioxidant characteristics, negative results have been obtained [2]. Studies have shown that using Vitamin E products is unnecessary to reduce cancer risk [2]. Conflicting results have been obtained in studies conducted on selenium which has another antioxidant characteristic. While in one study, it was shown that it reduces the prostate cancer risk by up to 50%, in another study, it was indicated that it does not reduce the prostate cancer risk [25, 26].

Obesity, together with a sedentary life-style, causes insulin resistance [2]. Cell growth and proliferation are triggered by chronic increased insulin level. It is considered that uncontrolled cell proliferation also affects prostate cancer risk and prognosis [2]. Besides, it is considered that it plays a part in cancer development in inflammatory cells released from adipose tissue.

Screening

In order that prostate cancer screening is valuable, it must reduce disease-specific morbidity and/or mortality by detecting cancer at an early stage [27]. Nevertheless, detection at an early stage may also not turn out to be clinically advantageous [27]. Increased prostate cancer detection does not affect the survival of some patients; in addition, examination and treatment may increase the risk of treatment-related morbidity in patients [27]. Scans can be performed with serum PSA and digital rectal examination (DRE) [27]. It has been observed that prostate cancer incidence increases prominently with screening by measuring the serum PSA level [27]. Especially there has been an increase in the detection of early-stage diseases [27]. However, when the long-term results of these screenings were examined, it has been observed that it does not affect survival [27].

Before deciding on screening, individuals should discuss the benefits and harms with their clinicians and include their own values and preferences in the decision [28]. Revised guidelines acknowledge that screening provides some men with small benefits to reduce the mortality risk from prostate cancer, many other men may be damaged from screening [28].

These include false-positive results that require additional analyses and possible prostate biopsy and redundant diagnosis and treatment cause treatment complications such as

incontinence and erectile dysfunction [28]. When determining whether screening is proper in individual cases, the patient's family history, race/ethnic origin, coexisting medical conditions, the benefits and harms of screening, and the values of treatment-specific outcomes and other health needs should be considered.

Clinical Findings, Diagnosis, Laboratory and

Imaging Symptoms and Findings:

Most prostate cancers are diagnosed by detecting the increase in serum PSA. Obstructive uropathy symptoms are observed due to hyperplasia of the prostate that occurs mostly in the same age group [12]. However, large or locally advanced prostate cancers can cause obstructive uropathy symptoms. Apart from this, patients may rarely consult with symptoms of urinary retention caused by epidural metastasis and cord compression, or with neurological symptoms [12]. Lymphedema based on lymph node metastases may be seen. Patients may consult with back pain or pathological fractures since the axial skeleton is the most common region of metastasis [12].

Laboratory Findings:

One of the most important tests is the serum PSA level. It is usually detected in patients at levels higher than 4 ng/mL. 50-70% of those who have a serum PSA value higher than 10 ng/mL are diagnosed with prostate cancer [12].

Serum PSA level, which is important for the diagnosis, is also used in the follow-up of the disease in advanced disease. In the assessment of treatment response, reductions in serum PSA are associated with good response [12].

In some cases with bone metastases, elevated serum Alkaline phosphatase (ALP) and calcium can be detected [12].

Prostate Biopsy:

Biopsy with transrectal ultrasonography (TRUS) is the gold standard in the diagnosis of prostate cancer [12]. In patients with abnormal DRE and/or increased serum PSA, Prostate biopsy specimens are obtained from the apex, middle, and base with TRUS [12]. Biopsy from a total of at least 10 areas is required for accurate diagnosis and staging.

Imaging:

Imagining methods for patients diagnosed with prostate cancer should be determined according to the risk of the disease [12]. In the case of a mildly elevated PSA, low Gleason score, and thought to be limited to the prostate by DRE and USG, additional imagining is not required [12]. Recently, multiparametric magnetic resonance imaging (MRI) has provided the opportunity to perform a more specific biopsy for patients with previously negative prostate biopsy [12]. MRI can also be used in the evaluation of local lymph node metastases. Since bone is one of the areas where prostate cancer most frequently metastasizes, conventional radionuclide (technetium-99) scans or PSMA-PET imaging are performed, especially in high-risk patients. Visceral organ metastases can be evaluated with computed tomography (CT) of the thorax and abdomen or PSMA-PET [12].

Treatment:

Treatment for prostate cancer should be planned according to the risk of the disease and the expected life expectancy of the patient. According to the American "National Comprehensive Cancer Network" (NCCN) guideline, the disease risk is evaluated in 5 categories very low, low, moderate, high, and very high [29]. The medium-risk group is further divided into two subgroups as good and bad. Risk classification is determined according to the T stage of the disease, histological grade, serum PSA level, number of positive prostate biopsies, tumor percentage, and tumor density [29].

Untreated observation or active surveillance may be effective management for appropriate, selected patients, typically at very low or low-risk levels and with a life expectancy of less than 10-15 years [29]. Active surveillance for such patients includes serial PSA measurements, DREs, and periodic prostate biopsies to reassess the extent and spread of cancer [29]. Radical prostatectomy or radiotherapy (RT) is a good option in low-risk patients in the local stage, with a life expectancy of more than 10-15 years [29]. For patients in the intermediate-risk group, surgery or RT treatment is preferred for those with a life expectancy of more than 10 years, while untreated observation or active surveillance may be an option for those with a life expectancy of less than 10 years [29]. A curative treatment should be applied in high or very high-risk patients with a life expectancy of more than 5 years. For those with a life expectancy of fewer than 5 years, observation, androgen deprivation therapy (ADT), or RT are among the treatment options [29].

ADT can be performed surgically (orchiectomy) or medically. For medical ADT,

luteinizing hormone-releasing hormone (LHRH) analogs are used. The goal of ADT is to keep the total testosterone level below 20 or 50 ng/dl (castrate level) [29]. ADT is used as an adjuvant after definitive treatment in locally advanced disease in the treatment of prostate cancer, as well as at every stage of treatment to provide disease control in advanced disease [29].

In a selected group of hormone-naive patients in advanced disease (with low metastatic tumor volume and limited metastasis), only ADT can be performed [29]. In fit patients who are hormone-naive but have a high tumor burden, the use of docetaxel or abiraterone acetate with ADT produces better results than the use of ADT alone [29]. Metastatic patients usually develop resistance to androgen deprivation within 12-18 months, despite treatment. The disease that progresses despite keeping testosterone levels below 20-50 ng/dl with ADT applied in metastatic disease is defined as castration-resistant prostate cancer (CRPC) [29].

In the treatment of metastatic CRPC, cytotoxic chemotherapies (Docetaxel or Cabazitaxel), hormonal treatments (Abiraterone Acetate and Enzalutamide) and active cellular immunotherapy (Spiuleucel-T) treatments can be applied [29]. Abiraterone Acetate, one of the hormonal treatments, inhibits the release of testosterone from the testicles and the release of androstenedione, DHEA, DHEA-S from the adrenal glands and prostate cancer cells, as an androgen biosynthesis inhibitor [29]. Enzalutamide, another hormonal treatment option, prevents testosterone from binding to the androgen receptor (AR), prevents its nuclear translocation, and binding to DNA, thus causing inhibition of multiple steps in the AR signaling cascade [29]. It inhibits the growth and reproduction of cancer cells. Guidelines state that any one of the treatments Docetaxel, Abiraterone Acetate, Enzalutamide, and Spiuleucel-T can be used in the primary treatment of metastatic CRPC [29].

RESOURCES

1. Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018; 68(issue): 394-424.
2. Rawla P. Epidemiology of Prostate Cancer. World J Oncol 2019; 10(issue): 63-89.
3. Herget KA, Patel DP, Hanson HA, et al. The recent decline in prostate cancer incidence in the United States, by age, stage, and Gleason score. Cancer Med 2016; 5(issue): 136-141.
4. Health Statistics Annual 2018 [Internet]. Directorate General for Health Information Systems, 2019. Accesed 14 June 2020. Available from: https://dosyasb.saglik.gov.tr/Eklenti/36134,siy2018trpdf.pdf?0.
5. Perdana NR, Mochtar CA, Umbas R, et al. The Risk Factors of Prostate Cancer and Its Prevention: A Literature Review. Acta Med Indones 2016; 48(issue): 228-238.
6. Taitt HE. Global Trends and Prostate Cancer: A Review of Incidence, Detection, and Mortality as Influenced by Race, Ethnicity, and Geographic Location. Am J Mens Health 2018; 12(issue): 1807-1823.
7. Survival Rates for Prostate Cancer [Internet]. American Cancer Society, 2018. Accesed 07 June 2020. Available from: https://www.cancer.org/cancer/prostate-cancer/detection-diagnosis-staging/survival-rates.html.
8. SEER Cancer Statistics [Internet]. 2018. Accesed 07 June 2020. Available from: https://seer.cancer.gov/explorer/application.php.
9. Epidemiology of prostate cancer in Europe [Internet]. European Commission, 2015. Accesed 07 June 2020. Available fromhttps://ec.europa.eu/jrc/en/publication/epidemiology-prostate-cancer-europe.
10. Markozannes G, Tzoulaki I, Karli D, et al. Diet, body size, physical activity and risk of prostate cancer: An umbrella review of the evidence. Eur J Cancer 2016; 69(issue): 61-69.
11. Cancer Stat Facts: Prostate Cancer [Internet]. SEER, 2018. Accesed 07 June 2020. Available from: https://seer.cancer.gov/statfacts/html/prost.html.
12. Schade G. Cancer. In: Papadakis MA, McPhee SJ, Rabow MW, editors. CURRENT Medical Diagnosis and Treatment 2020. 59 th ed. McGraw-Hill Education, 2019. p. 1674-1675.
13. Parker PM, Rice KR, Sterbis JR, et al. Prostate cancer in men less than the age of 50: a comparison of race and outcomes. Urology 2011; 78(issue): 110-115.
14. Okobia MN, Zmuda JM, Ferrell RE, et al. Chromosome 8q24 variants are associated with prostate cancer risk in a high-risk population of African ancestry. Prostate 2011; 71(issue): 1054-1063.

15. Mucci LA, Hjelmborg JB, Harris JR, et al. Familial Risk and Heritability of Cancer Among Twins in Nordic Countries. JAMA 2016; 315(issue): 68-76.
16. Gallagher DJ, Gaudet MM, Pal P, et al. Germline BRCA mutations denote a clinicopathologic subset of prostate cancer. Clin Cancer Res 2010; 16(issue): 2115-2121.
17. Chen YC, Page JH, Chen R, et al. Family history of prostate and breast cancer and the risk of prostate cancer in the PSA era. Prostate 2008; 68(issue): 1582-1591.
18. Chu LW, Ritchey J, Devesa SS, et al. Prostate cancer incidence rates in Africa. Prostate Cancer 2011; 2011(issue): 947870.
19. Hsing AW, Tsao L, Devesa SS. International trends and patterns of prostate cancer incidence and mortality. Int J Cancer 2000; 85(issue): 60-67.
20. Venkateswaran V, Klotz LH. Diet and prostate cancer: mechanisms of action and implications for chemoprevention. Nat Rev Urol 2010; 7(issue): 442-453.
21. Gibson TM, Ferrucci LM, Tangrea JA, et al. Epidemiological and clinical studies of nutrition. Semin Oncol 2010; 37(issue): 282-296.
22. Rohrmann S, Platz EA, Kavanaugh CJ, et al. Meat and dairy consumption and subsequent risk of prostate cancer in a US cohort study. Cancer Causes Control 2007; 18(issue): 41-50.
23. van Breemen RB, Pajkovic N. Multitargeted therapy of cancer by lycopene. Cancer Lett 2008; 269(issue): 339-351.
24. Erdman JW, Jr., Ford NA, Lindshield BL. Are the health attributes of lycopene related to its antioxidant function? Arch Biochem Biophys 2009; 483(issue): 229-235.
25. Yoshizawa K, Willett WC, Morris SJ, et al. Study of prediagnostic selenium level in toenails and the risk of advanced prostate cancer. J Natl Cancer Inst 1998; 90(issue): 1219-1224.
26. Lippman SM, Klein EA, Goodman PJ, et al. Effect of selenium and vitamin E on risk of prostate cancer and other cancers: the Selenium and Vitamin E Cancer Prevention Trial (SELECT). JAMA 2009; 301(issue): 39-51.
27. Ilic D, Neuberger MM, Djulbegovic M, et al. Screening for prostate cancer. Cochrane Database Syst Rev 2013: Cd004720.
28. Schade G. Cancer. In: Papadakis MA, McPhee SJ, Rabow MW, editors. CURRENT Medical Diagnosis and Treatment 2020. 59 th ed. McGraw-Hill Education, 2019. p. 1676-1678.
29. NCCN Clinical Practice Guidelines in Oncology, Prostate cancer Verison 2.2020 [Internet]. NCCN, 2020. Accesed 8 June 2020. Available from: https://www.nccn.org/professionals/physician_gls/default.aspx#prostate.

2.4. Colorectal Cancer (See Section 4)

2.5. Thyroid Cancer

Three types of thyroid cancer develop from the thyroid follicle epithelium. These are papillary thyroid cancer (PTC), follicular thyroid cancer (FTC), and anaplastic cancers. Despite the many biological differences between them, PTC and FTC are known as differentiated thyroid cancers (DTC) and their treatment is similar. Therefore, they will be examined under the same title. Medullary cancers and anaplastic cancers arising from parafollicular C cells of the thyroid constitute the group of undifferentiated thyroid cancers.

Differentiated Thyroid Cancers

PTC accounts for approximately 85% of all thyroid cancers. The incidence of FTC is around 12%. The incidence of DTC has been increasing worldwide for the last 3 decades [1- 3]. It has been reported that FTC is more common, especially in endemic iodine deficiency regions in sub-Saharan Africa [4]. Increases in the incidence of thyroid cancer are striking all over the world. Between 1990 and 2013, the incidence of thyroid cancer increased by 33% in low-income countries and 19% in high-income countries [5]. Turkey, with an incidence rate of 7.8% per hundred thousand people, is among the countries with a high incidence rate, such as North America, China, Australia, Italy, Germany, and Ukraine. Mortality rates due to thyroid cancer vary between 0.5-0.7/year per hundred thousand people [6].

TPCs are histologically recognized by papillary structures formed by tumor cells surrounded by a fibrovascular sheath. They are non-encapsulated tumors and may contain partially cystic areas. They do not contain follicles and colloidal material. They are known for their large and oval-shaped nucleus and powdery chromatin structures. The appearance of calcified psammoma particles formed by papillary structures that are not nourished is quite pathognomonic. They often form multifocal foci within the thyroid gland; this is explained by intraglandular metastases. Apart from this classic variant of papillary carcinomas, there are also variants such as a follicular, tall cell (it is an aggressive form and accounts for about 1% of papillary cancers), insular and diffuse sclerosing. Although papillary microcarcinomas are not technically a specific variant, they represent papillary carcinomas that are 1 cm and smaller. In addition to this pathological typing, the patient's age, tumor size, the potential of

invasion and metastasis are parameters that determine the prognosis of papillary cancers. Disease-specific mortality increases with patient's age and tumor size.

Histologically, follicular thyroid cancers are characterized by the formation of follicular structures by epithelium, the presence of colloidal material, nuclear atypia, and vascular and/or capsular invasion. They occur at a later age compared to papillary cancers. Tumor size, patient age, degree of invasion, and grade are factors that determine prognosis. Variants with hurthle cells and insular variants are known to have a worse prognosis [7].

Screening

Although the incidence of DTC is increasing, no screening method is recommended for screening adult patients in American and European guidelines [8]. In the presence of pathologies such as PTEN mutation, Cowden's disease, Familial Adenomatous Polyposis (FAP) syndrome, Carney Complex disease, Multiple Endocrine Neoplasia (MEN) type 2 syndromes, and Werner's syndrome, which have been detected in their first-degree relatives in connection with DTC, individuals can be screened on this basis. Since there are no reports that screening prevents or reduces recurrence and death in familial DTC patients, history and neck examination should be carefully done in the ordinary health examinations of such individuals [9].

Risk Factors

Familial predisposition and obesity have been identified as risk factors for thyroid cancers. The concept of over-screening/diagnosis, which can be defined as the unnecessary discovery and efforts for treatment of a tumor that is not expected to become symptomatic, has been discussed in recent years. However, it should not be forgotten that this concept is applicable mostly for high-income countries and it cannot be generalized to our country and the whole world. Factors such as exposure to radiation (especially the processes related to the diagnosis and treatment of childhood cancers), fire retardants, iodine supplementation, and exposure to volcanic ash have been defined as environmental risk factors.

Familial Predisposition

Familial predisposition and genetic predisposition play an important role, especially in the etiology of medullary thyroid cancers. When the comprehensive studies on this subject are examined, it is understood that familial predisposition should be considered as a risk

factor also for thyroid cancers other than medullary cancers. It is stated that the incidence of non-medullary thyroid cancer can increase up to 3 times in people with a family history [10].

Over Examination/Screening

Excessive and over-use of diagnostic tools such as ultrasonography (USG) and Fine Needle Aspiration Biopsy (FNAB) increases the diagnosis of DTC [11,12]. Authors who consider this as a 'problem' argue that the treatments applied after detecting small nodules of no clinical significance, performing a biopsy, and reporting them as malignant do not contribute to survival or recurrence. However, the increase in disease-related death rates with increasing incidence suggests that over examination and screening may not play at least a fundamental role in the increase in incidence [13]. Community-based screening programs for thyroid cancer are not implemented; however, it is not an acceptable approach not to investigate a clinically and radiologically suspicious thyroid nodule even if it is detected incidentally. It should not be forgotten that each type of thyroid cancer has subtypes that have very different clinical behaviors and can be life-threatening.

Obesity

Obesity has become a social health problem increasing globally, and there are speculations that it may be associated with increased DTC [14]. In studies reported from South Korea and Europe, a relationship is observed between high body mass index (BMI) and the detection of malignant aspirate in FNAB. A similar relationship is also obtained with anthropometric values such as wider waist circumference and high-fat ratio. These results are mostly valid for the female population, and the relationship between obesity and DTC in men is much more controversial [15-17]. In a retrospective analysis, the relationship between BMI and recurrent disease and poor prognosis is also demonstrated [18]. Although the mechanism by which obesity affects DTC is not known, increased insulin resistance, estrogen hormone, and inflammation may be responsible.

Exposure to Radiation

Exposure to radiation is the most important known environmental cause of thyroid cancer worldwide. The thyroid gland is the main source of cancers that develop as a result of exposure to radiation, especially in childhood and adolescence [19]. Incidents such as the nuclear accident in Ukraine's Chernobyl reactor in 1986, the atomic bombing of the Japanese

cities of Hiroshima and Nagasaki in 1945, and the nuclear accident in the Three Miles Island of the United States (USA) in 1979 showed that the risk of thyroid cancer, especially in the adolescent and childhood population, has increased many times after exposure to nuclear material [20]. With the introduction of Computed Tomography (CT) in the 1970s, it was understood that imaging for medical purposes poses a risk for DTC, especially for adolescents and children [21].

Fire retardants

These chemicals, which are extensively used in the electronics and furniture industries, are used to meet the standards in especially inflammable/flammable products, and the most common examples are polybrominated diphenyl ether (PBDE). These substances are considered to cause thyroid cancer. PBDE has been shown to cause thyroid hormone disturbance [22].

Volcanic Ash

In studies conducted on Hawaii and Icelandic islands, a relationship was established between volcanic ash and DTK. In addition to this, the incidence of thyroid cancer was found to be high in regions known to have high volcanic activity, such as Vanatu, French Polynesia, and New Caledonia [23]. The island of Sicily is home to Mount Etna, one of the most active volcanic formations in Europe. In the population settled around this mountain in the Catania region of Sicily, the incidence of DTC is higher than in the urbanized regions of the island. The reason for this increase seen in volcanic regions may be the high amount of heavy metals in the region. The fact that heavy metals have carcinogenic properties and they cause genetic alterations and mutations, and regional radioactivity can be blamed as causes of increased DTC. In addition to all these, the fact that the same rate is not observed in all volcanic active regions in our world brings to mind the issue that the increased DTC rate may be related to the volcanic content [24].

Differentiated Thyroid Cancers in Childhood

Differentiated thyroid cancers in childhood can be handled differently from adults, especially because there are some basic differences in the course of the disease. Some part of DTC seen in childhood develops secondary to the radiation used in the treatment of other cancers seen in this period and may have a worse course than adult DTC. The pathological

classification is the same as the criteria approved by the World Health Organization (WHO) for adults [25]. In childhood, 90% of cases are PTC. The detection rate of malignancy in thyroid nodules in childhood is higher compared to adults. Additionally, regional lymph node involvement, pulmonary metastasis, and extrathyroidal spread are also more common in DTCs in childhood. Despite this, the prognosis is much better than adults at similar stages. FTC has a better prognosis than PTC in childhood, with a lower probability of advanced disease at diagnosis. Although there is not much difference between adults and children in the approach to thyroid nodules, especially nodule size should be considered less in terms of FNAB requirement. Rather, the ultrasonographic features of the nodule (such as the blood pattern, contours, presence of microcalcification) should be considered when making an FNAB decision [26].

Approach to thyroid nodules

Thyroid cancers manifest themselves as nodules in the thyroid gland. It should be noted that only 4-6.5% of thyroid nodules are thyroid cancer. It is clinically important to be able to distinguish thyroid cancers from benign thyroid nodules and treat them. As thyroid nodules are very common in the population, a population-based thyroid cancer screening is not a cost-effective method and has no practical examples. However, the prevalence of thyroid cancer is higher in some groups. These groups are people who have been exposed to radiation in the head and neck region and people with a family history of thyroid cancer, especially medullary cancer. These groups can be followed within the concept of opportunistic screening in 2nd and 3rd level health institutions [27].

Thyroid ultrasonography (USG) should be performed after a detailed anamnesis and physical examination for a person with clinical suspicion of a thyroid nodule. The only hormone whose outcome needs to be known is thyroid-stimulating hormone (TSH). Findings suggestive of a hard and fixed mass in the thyroid, respiratory tract obstruction symptoms, cervical lymphadenopathy, and vocal cord paralysis in the physical examination are interpreted in favor of thyroid cancer. If TSH levels are normal or high, the most valuable method for diagnosis is pathological evaluation of the nodules with fine-needle aspiration biopsy (FNAB). TSH level is a parameter not associated with thyroid cancer. Although the radiological character of the nodules in USG gives information about the nodules that require FNAB, it alone is not sufficient to make a decision for surgery. In order to increase the

diagnostic value of FNAB, it is more valuable to perform this intervention with USG. Although it is generally accepted that only nodules larger than 1 cm should be evaluated in the clinic because of the potential for malignancy, it should not be forgotten that the radiological features of the nodule are more valuable than its size, in terms of malignancy criteria.

Although nodules with irregular borders, microcalcifications, and a longer dimension than the width are particularly suspicious for thyroid cancer, FNAB should be performed on all solid and hypoechoic thyroid nodules larger than 1 cm. FNAB should be performed for all nodules that have sonographic criteria for malignancy, regardless of size. In addition, individuals with family history and those who received radiation to the head and neck region in childhood should have FNAB performed even if their nodules are smaller than 1 cm. Nodules smaller than 1 cm that are not sonographically suspicious (isoechoic, hyperechoic, cystic) can be followed. If a change in nodule character and increase in size is detected, FNAB should be performed or repeated [28–33].

Follicular thyroid cancers typically occur as a thyroid nodule. FNAB cannot distinguish between FTC and follicular adenomas by itself. For the diagnosis of FTC to be made, it must be shown in the thyroidectomy specimen that the tumor has invaded the capsule or vascular. Nonpalpable nodules detected during ultrasonography or other imaging methods are called “incidentally detected nodules” or “incidentalomas”. “Nonpalpable nodules” carry the same degree of malignancy-risk as palpable nodules of the same size. Incidental thyroid nodules are found in 1-2% on average of patients who undergo 18FDG-Positron emission tomography (PET) screening for other reasons. Because of the high- risk of malignancy in nodules that hold high levels of 18FDG in PET examination, such lesions should also be evaluated. FNAB should be performed on sonographically suspicious nodules in patients with multinodular goiter (MNG). If there is no highly suspicious nodule, FNAB should be done on the dominant nodule with the largest size. Biochemical tests such as anti-thyroid peroxidase (TPO) antibodies or thyroglobulin to elucidate thyroid nodules do not contribute to the diagnosis [34-36].

Treatment of differentiated thyroid cancers

Surgery is the treatment for those diagnosed with “malignancy” or “suspicious cytology for malignancy” with the result of FNAB performed for thyroid nodule. The patient

should certainly be evaluated with neck and thyroid USG before the operation in order to determine the surgical area. In preoperative evaluation, Computed Tomography (CT), Magnetic Resonance Imaging (MRI), and 18 FDG-PET may also be rarely required [37].

Surgical Treatment

The aim of surgical treatment is to remove all of the tumor and thyroid tissue if possible, not to leave metastatic lymph nodes in the neck, and if soft tissue invasion is considered, also to remove these areas. Total thyroidectomy (TTx) and central lymph node dissection (CLND) are required in patients with extrathyroidal extension or metastases identified in lymph nodes or distant metastases. In patients with tumors larger than 4 cm, if preoperative suspicious lymph nodes are detected in the central region, bilateral CLND should be added to TTx.

TTx is sufficient in patients with a tumor larger than 1 cm but smaller than 4 cm, without extrathyroidal extension, and without clinically detected lymph node metastasis. Different guidelines suggest that lobectomy can also be performed in this group of patients with low-risk papillary and follicular carcinomas [38]. However, TTx may be recommended for these patients, considering the possibility of patients dropping out of follow-up, the necessity of lifelong radiological follow-up after lobectomy, and the fact that follow-up will be easier and safer after TTx [37].

Low-risk patients with tumors smaller than 1 cm should preferably be operated on first by lobectomy. In patients with a tumor smaller than 1 cm, unifocal, without extrathyroidal invasion and clinical lymph node metastasis, lobectomy is sufficient if there is no history of head and neck radiotherapy (RT), familial history of thyroid cancer, and no clear indication for removal of the contralateral lobe. Except for patients with significant comorbid conditions, advanced age, and/or patients who cannot be operated for non-thyroid reasons, it is appropriate for all patients diagnosed with DTC to be operated on.

In addition, the prognosis of follicular variant papillary cancer (EFVPTC) without capsular or vascular invasion is very good, and it has recently been suggested that it should not be considered "cancer" and its histopathological naming should be changed to "noninvasive follicular thyroid neoplasia (NIFTP) with papillary-like nuclear features".

The prophylactic central lymph node dissection (CLND) approach is still controversial. TTx is sufficient for PTC and most follicular cancers with no T1 or T2 tumors

with poor prognostic features, and no clinically metastatic lymph nodes. However, it should not be forgotten that some of the T1 and T2 tumors may also have central lymph node metastasis. In patients with clinically lateral lymph node involvement in T3 and T4 tumors, ipsilateral or bilateral prophylactic CLND should be performed even if central region lymphadenopathy (LAP) is not observed. In the presence of proven metastatic involvement in the central or lateral neck compartments preoperatively and/or suspected during surgery, therapeutic dissection of the relevant compartments should be performed. In thyroid cancer surgery, functional compartment dissection should be performed instead of removing the metastatic lymph nodes one by one ("pick up").

In patients with tumor detected after lobectomy, if tumor diameter is larger than 1 cm, if the multifocal tumor, extrathyroidal spread, vascular invasion, lymph node metastasis, distant metastasis, history of RT to head and neck or histopathological subtypes indicating unfavorable prognosis is present, complementary thyroidectomy should be performed and in patients with clinical involvement, therapeutic CLND should also be performed.

Postoperative Assessment

After surgery, pathological evaluation and staging should be done. Since the AJCC/TNM staging system shows the risk of mortality, it is also recommended to make also the classification recommended by the American Thyroid Association (ATA) of low, intermediate, and high-risk patients in determining the risk of DTC relapse or recurrence [39]. Postoperative risk assessment is a guide in predicting prognosis as well as for deciding on radioactive iodine (RAI) treatment after surgery and determining the level of TSH suppression.

Radioactive Iodine Treatment (RAI)

After surgery, RAI treatment can be used to ablate residual tissue,

to reduce relapse/mortality, and for treatment (in patients with persistent disease). Before this treatment, the patient's TSH level should be above 30 mU/mL. There are different methods to create endogenous hypothyroidism. RAI therapy can be applied starting from four to six weeks after surgery. TSH, Thyroglobulin (Tg), and anti-Tg should be measured in all patients before the therapeutic dose is given. Tg is known to be an important prognostic factor. Patients who will receive RAI treatment should be protected from drugs with radiocontrast and high iodine content. In patients who will have postoperative RAI applied

for the first time, an iodine involvement examination can be performed with a very low dose of ^{131}I to determine the degree of involvement in the thyroid bed. However, its usefulness is still controversial. Instead, it is recommended to evaluate the presence of residual tissue with neck US and/or 99mTc scintigraphy after the first month postoperatively,

After a therapeutic dose of RAI is given, whole-body scan (WBS) should be done between the 5th and 8th days. WBS is valuable in detecting lymph node involvement and distant metastases, especially in patients with less than 2% involvement in the thyroid region. In this case, WBS after ^{131}I treatment will give precise information about the exact stage of the disease, with the exception of rare radioresistant tumors. The recommended dose of RAI in low-risk and intermediate-risk patients for ablation of residual tissue is 30 mCi. In the presence of residual tumor, recommended doses are 100-200 mCi. Generally, 150 mCi dose is preferred in the presence of lymph node metastases, and 200 mCi dose is preferred in the presence of organ metastases.

Complications that may develop in the early period due to RAI treatment can be summarized as, in addition to radiation thyroiditis, changes or loss of taste sensation, sialadenitis, nausea, and vomiting due to radiation sickness [40].

Early Follow-up

After surgery and, if necessary, RAI treatment, the dose of thyroid hormone (LT4) should be adjusted according to the patient's risk group. After initial therapy, in adjusting the LT4 dose, the target TSH for the first year should be between 0.5-2 mU/mL in low-risk patients who have undergone TTx, received ablation therapy or not, Tg below 0.2 ng/ml, or undergone lobectomy.

It should be between 0.1-0.5 mU/mL in low-risk patients and intermediate-risk patients and less than 0.1 mU/mL in high-risk patients, with mild Tg positivity or no

ablation therapy and measurable Tg levels despite receiving ablation therapy In high-risk patients, sT3 and sT4 should be within normal limits, and iatrogenic thyrotoxicosis should not be caused in the patient.

After the appropriate dose is achieved, TSH measurements should be repeated every 6-12 months. Serum Tg concentration is used as a tumor marker in DTC follow-up. During follow-up, anti-Tg should also be measured at intervals of 6-12 months, depending on the patient's degree of risk. Persistent anti-Tg antibody positivity should be interpreted as a sign

of ongoing disease or relapse. Since Tg cannot be used safely in anti-Tg antibody positivity, neck the US and WBS can be used in the follow-up. CT, MRI, 18FDG-PET/CT methods can be used in suspicion of metastasis [41].

In the long-term postoperatively, it has been suggested to evaluate the response of patients to treatment in four groups: excellent, biochemically inadequate, structurally inadequate, and indeterminate [38].

Doubling time of basal Tg levels (<1 year, 1-3 years, or >3 years) or rate of increase in basal Tg (≥0.3 ng/mL/year), defines patients at increased risk for the development of structurally demonstrable local regional disease or distant metastasis.

Long Term Follow-up

Long-term follow-up of DTC is done with annual physical examination (PE), TSH, Tg, and anti-Tg measurements under LT4 treatment, and neck the US. In the presence of changes that indicate local recurrence or distant metastasis, treatment options such as surgery, RAI, RT, multikinase inhibitors are evaluated according to the patient, according to the data of stimulated Tg and/or TVT and, if necessary, advanced imaging methods (CT, MRI, 18FDG-PET/CT) [41].

In the low-risk group, if remission is confirmed by the assessment made after the initial treatment, it is recommended to keep the TSH in the 0.5-2mU/mL range. In the intermediate-risk group, in patients with excellent response, LT4 dose reduction is recommended with a TSH target of 0.5-2 mU/mL. In the high-risk group, it is recommended to remove complete suppression, but keep TSH between 0.1-0.5 mU/mL for at least five years in patients who are considered to have excellent response according to the stimulated Tg level in the evaluation made between 9-12 months after the first treatment. [38]. Tg levels should be measured at least every 6-12 months during years in all biochemically deficient, structurally deficient ones, or with indeterminate responses. In patients with a structurally inadequate response, TSH should always be kept below 0.1 mU/mL.

The use of LT4 at doses to cause subclinical thyrotoxicosis in the treatment of DTC may trigger cardiac complications (supraventricular arrhythmias, left ventricular hypertrophy, exacerbation of ischemic heart disease), prothrombotic process and bone loss. In the long-term follow-up of the patients, neck USG is the most sensitive method in evaluating the remaining or recurrent disease. Together with USG-guided FNAB and

cytology, Tg measurement in aspiration fluid is a valuable guide.

Those with Recurrent and Metastatic Diseases

In diffuse recurrent nodal disease, when airway or esophageal invasion is suspected, CT or MRI with or without contrast can be performed in nodal recurrences, where neck USG cannot evaluate adequately. In high-risk patients, non-contrast thoracic CT can be performed to view the pulmonary parenchyma independent of RAI imaging. Contrast-enhanced thorax CT can be performed to evaluate the mediastinum. 18FDG-PET/CT, brain MRI, abdominal CT/MRI, and bone scintigraphy can be performed in high-risk patients with negative neck and thorax imaging results, with a Tg level above 10 ng/mL or with progressively elevated anti-Tg antibodies.

Surgical and RAI treatment options can be used to treat relapse in the neck region [41]. In patients for whom surgical excision is not possible, RT can be applied, especially for those over the age of 45, if the involvement of RAI in the tumor tissue is low. In the presence of lung metastases, it is recommended to give RAI as long as ^{131}I involvement is present. The doses to be chosen may be 200 mCi or higher and safer doses calculated according to 'dosimetry' [40]. As long as iodine involvement continues, it is recommended that new doses should not be given before 6 months for the first 2 years. A significant decrease in serum Tg levels and/or a decrease in the size of metastases or a slowed growth rate are taken into account in evaluating treatment response.

^{131}I therapy has no upper dose limit. It can be applied as long as there is RAI involvement and there is a benefit. In some patients, it may be necessary to give RAI over 1,000 mCi in total. However, it should be noted that there is an increase in the frequency of leukemia and secondary cancers after 600 mCi [40]. In addition, empirical doses of more than 150 mCi at one time
should be avoided in patients over 70 years of age. Salivary gland damage or nasolacrimal duct obstruction is more common after repeated doses of RAI. Considering that doses of 400 mCi and above may cause hypospermia, it may be recommended to store sperm in male patients and ovum in females before repeated treatment. In cases where tumor differentiation is lost, Tg synthesis may decrease, in addition to the loss of iodine involvement. Therefore, decreased RAI involvement and no decrease in tumor size or growth, although there is a decrease in serum Tg levels, indicate resistance to RAI treatment. Resistance to RAI treatment is seen in 15-20% of DTCs.

^{131}I can be used in the treatment of bone metastasis or RT can be used for palliative purposes and pain control. In bone metastases, surgery can be performed if the lesion is suitable and isolated for surgical excision, otherwise bisphosphonate infusion, denosumab, embolization or bone cement injection can be performed. In patients with extensive bone metastases, even if they are to be given or receiving tyrosine kinase inhibitor (TKI) therapy, zoledronic acid iv. infusion therapy is recommended to be applied quarterly [42]. Brain metastases are rare. Surgical excision may be selected when appropriate, and external RT may be selected for those who cannot be surgically removed and RAI is not useful. In bone or brain metastases with compression symptoms, glucocorticoid administration during RAI or external RT are recommended.

Structurally seen RAI-resistant DTC are classified into four groups;

a) Malignant/metastatic tissue never keeps RAI.

b) Although it previously kept RAI, it no longer has RAI involvement.

c) Some lesions keep RAI, while others do not.

d) Although metastatic disease keeps a significant level of RAI, it progresses. There is no point in giving RAI treatment anymore to these patients. Patients with RAI-resistant metastatic DTC,

but who are asymptomatic, stable, or minimally progressive can be followed under TSH suppression.

In progressive patients, after determining the level of progression by 18FDG-PET/CT, CT, MRI, switching to systemic and/or directed therapies should be considered if there is an increase of more than 20% in the sum of the longest diameters of the target lesions, new metastatic lesions appear and new disease-related symptoms appear.

In recent years, with a better understanding of the molecular mechanisms of thyroid carcinogenesis, the use of drugs that inhibit the activity of the tyrosine kinase receptor and create an antiproliferative effect has brought a new dimension to systemic therapy in RAI-resistant DTC. There are phase II studies completed with axitinib, dovitinib, motesanib, pazopanib, selumetinib, sunitinib, vandetanib, and phase I studies completed with cabozantinib. In patients using TKI, although the growth of the tumor is prevented for months by drug use, regrowth may occur later and its reason is thought to be resistance to TKI. However, the overall survival effect of TKIs has not been demonstrated and they also

have serious side effects [42].

Although cytotoxic chemotherapy in the form of doxorubicin or a combination of doxorubicin and cisplatin is currently recommended in patients who do not respond to TKI and in poorly differentiated thyroid cancer, response rates are around 10-20%. Experimental studies using angiogenesis inhibitors, immunomodulatory drugs, apoptosis triggers, and gene therapy studies are continuing.

RESOURCES

1. European Network of Cancer Registries Factsheets. https://www.encr. eu/sites/default/files/factsheets/ENCR_Factsheet_Thyroid_2017.
2. Kitahara CM, Sosa JA. The changing incidence of thyroid cancer. Nat Rev Endocrinol 2016; 12(11): 646–653.
3. Dal Maso L, Tavilla A, Pacini F, et al. Survival of 86,690 patients with thyroid cancer: a population-based study in 29 European countries from EUROCARE-5. Eur J Cancer 2017; 77: 140–152.
4. Quayson, JN, Clegg-Lamptey EK, Wiredul R, et al. Thyroid Disorders in Accra, Ghana: A Retrospective Histopathological Study at the Korle-Bu Teaching Hospital Journal of Medical and Biomedical Sciences 2013; 2(1): 1-7.
5. Fitzmaurice, C. The global burden of cancer 2013. JAMA Oncol 2015; 1:505–527.
6. Kim J, Jessica E, Gosnell A. Geographic influences in the global rise of thyroid cancer Nature 2020; 16:72-81.
7. Bryan R. Erik K. Alexander C, et al. 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer Thyroid 2016; 26:20-26.
8. Filetti S, Durante C, Hart D. Thyroid cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up Annals of Oncology 2019; 30: 1856–1883.
9. Richards ML. Familial syndromes associated with thyroid cancer in the era of personalized medicine. Thyroid 2010; 20:707–713.
10. Fallah M. Risk of thyroid cancer in first-degree relatives of patients with non-medullary thyroid cancer by histology type and age at diagnosis: a joint study from five Nordic countries. J. Med. Genet 2013; 50: 373–382.
11. Ahn HS, Kim, HJ, Welch, HG. Korea's thyroid-cancer 'epidemic' — screening and overdiagnosis. N. Engl. J. Med 2014; 371:1765–1767.
12. Vaccarella S. World wide thyroid-cancer epidemic? The increasing impact of overdiagnosis. N. Engl. J. Med 2016; 375:614–617.

13. Lim, H, Devesa S, Sosa, JA, Check D, Kitahara C. Trends in thyroid cancer incidence and mortality in the United States JAMA 2017; 317:1338–1348.
14. Nig, M. Global, regional, and national prevalence of over weight and obesity in children and adults during 1980–2013: a systematic analysis for the global burden of disease study Lancet 2014; 384:766–781.
15. Han JM. Obesity is a risk factor for thyroid cancer in a large, ultrasonographically screened population. Eur. J. Endocrinol 2013; 168:879–886.
16. Rinaldi S. Body size and risk of differentiated thyroid carcinomas: findings from the EPIC study. Int. J. Cancer 2012;131: 1004–1014.
17. Engeland A, Tretli S, Akslen LA, Bjørge T. Body size and thyroid cancer in two million Norwegian men and women. Br. J. Cancer 2006;95: 366–370.
18. Trésallet C. The incidence of papillary thyroid carcinoma and outcomes in operative patients according to their body mass indices. Surgery 2014; 156: 1145–1152.
19. Refetoff S. Continuing occurrence of thyroid carcinoma after irradiation to the neck in infancy and childhood. N. Engl. J. Med 1975; 292:171–175.
20. Heidenreich WF. Time trends of thyroid cancer incidence in Belarus after the Chernobyl accident. Radiat. Res 1999; 151:617–625.
21. Mathews D. Cancer risk in 680,000 people exposed to computed tomography scans in childhood or adolescence: data linkage study of 11 million Australians. BMJ 2013; 346:2360.
22. Mughal B, Demeneix A. Endocrine disruptors: flame retardants and increased risk of thyroid cancer. Nat. Rev. Endocrinol 2017; 13: 627–628.
23. Kung M, Nig, L, Gibson B. Volcanoes and carcinoma of the thyroid: a possible association. Arch. Environ. Health 1981; 36:265–267.
24. Ferlay J. Global cancer observatory: cancer today. Available at: https://gco.iarc.fr/. (Accessed: August 2019).
25. DeLellis RA, Lloyd RV, Heitz PU, Eng C. Pathology and Genetics of Tumours of Endocrine Organs World Health Organization Classification of Tumours, Volume 8. IARC Press, Lyon, France 2004
26. Monaco SE, Pantanowitz L, Khalbuss WE, et al. Cytomorphological and molecular genetic findings in pediatric thyroid fine-needle aspiration. Cancer Cytopathol 2012; 120:342–350.
27. Haugen BR, Alexander EK, Bible KC, et al. 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. Thyroid 2016; 26:1.

28. Nam-Goong IS, Kim HY, Gong G, et al. Ultrasonography-guided fine-needle aspiration of thyroid incidentaloma: correlation with pathological findings. Clin Endocrinol. 2004; 60:21.
29. US Preventive Services Task Force, Bibbins-Domingo K, Grossman DC, et al. Screening for Thyroid Cancer: US Preventive Services Task Force Recommendation Statement. JAMA 2017; 317:1882.
30. Marqusee E, Benson CB, Frates MC, et al. Usefulness of ultrasonography in the management of nodular thyroid disease. Ann Intern Med 2000; 133:696.
31. Tang AL, Falciglia M, Yang H, et al. Validation of American Thyroid Association Ultrasound Risk Assessment of Thyroid Nodules Selected for Ultrasound Fine-Needle Aspiration. Thyroid 2017; 27:1077.
32. Brito JP, Ito Y, Miyauchi A, Tuttle RM. A Clinical Framework to Facilitate Risk Stratification When Considering an Active Surveillance Alternative to Immediate Biopsy and Surgery in Papillary Microcarcinoma. Thyroid 2016; 26:144.
33. Tessler FN, Middleton WD, Grant EG, et al. ACR Thyroid Imaging, Reporting and Data System (TI-RADS): White Paper of the ACR TI-RADS Committee. J Am Coll Radiol 2017; 14:587.
34. Durante C, Grani G, Lamartina L, et al. The Diagnosis and Management of Thyroid Nodules: A Review. JAMA 2018; 319:914.
35. Burch HB, Burman KD, Cooper DS, et al. A 2015 Survey of Clinical Practice Patterns in the Management of Thyroid Nodules. J Clin Endocrinol Metab 2016; 101:2853.
36. Huang TW, Lai JH, Wu MY, et al. Systematic review of clinical practice guidelines in the diagnosis and management of thyroid nodules and cancer. BMC Med 2013; 11:191.
37. Murat Faik Erdogan, Mehtap Cakır, Alptekin Gursoy, et al. Association of Endocrinology and Metabolism, Thyroid Diseases Diagnosis and Treatment Guide 2019. ISBN: 978-605-4011-37-7
38. Haugen BR, Alexander EK, Bible KC, et al. 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. Thyroid. 2016;26(1):1-133.
39. Momesso DP, Vaisman F, Yang SP, et al. Dynamic Risk Stratification in Patients with Differentiated Thyroid Cancer Treated Without Radioactive Iodine. J Clin Endocrinol Metab 2016; 101:2692-700.
40. Freitas J, McDougall IR, Dauer LT, et al. American Thyroid Association Taskforce On Radioiodine Safety. Radiation safety in the treatment of patients with thyroid diseases by radioiodine 131I: practice recommendations of the American Thyroid Association. Thyroid. 2011;21(4):335-46.

41. Tufano RP, Clayman G, Heller KS, et al. Management of recurrent/persistent nodal disease in patients with differentiated thyroid cancer: a critical review of the risks and benefits of surgical intervention versus active surveillance. Thyroid. 2015;25(1):15-27.
42. Viola D, Valerio L, Molinaro E, et al. Treatment of advanced thyroid cancer with targeted therapies: ten years of experience. Endocr Relat Cancer 2016; 23:185-205.

Undifferentiated Thyroid Cancers

Medullary Thyroid Cancer

It is a neuroendocrine tumor sourcing from the parafollicular or C cells of the thyroid gland. It is characterized by the production of calcitonin and constitutes 1-2% of all thyroid cancers [1]. The majority of them occur sporadically, but up to 25% show familial inheritance as part of the Multiple Endocrine Neoplasia (MEN) 2 syndrome. Sporadic medullary thyroid carcinoma (MTC) typically occurs in the 4th-6th decades of life. They most commonly occur as a solitary thyroid nodule. Since parafollicular C cells are located in the upper pole of the thyroid gland, the nodules are also located in the upper pole. The rate of cervical lymph node metastasis at the time of diagnosis is quite high (approximately 70%). Again, 10-15% of patients have findings of dysphagia or hoarseness, suggesting an invasion of the upper airway or digestive tract. The rate of distant metastasis at the time of diagnosis is 5-10% [2,3]. The liver, lungs and bones are the organs where the disease most commonly metastasizes. Cervical lymph node metastasis rate is higher in multifocal disease [4].

In advanced disease, circles and flushing can be seen with the effect of hormones such as calcitonin and calcitonin gene-related peptides, secreted from the tumor. Rarely, there may be findings of Cushing's syndrome due to adreno-corticotropic hormone (ACTH) secretion. Most MTCs also secrete carcino-embryonic antigen (CEA). CEA can be used as a tumor marker in the diagnosis and follow-up of the disease. On the other hand, thyroid function tests (TFT) are mostly normal.

MEN2 syndrome is a syndrome resulting from different mutations in the RET proto-oncogene and showing an autosomal dominant inheritance. It has two subtypes, MEN2A and MEN2B, and both are associated with MTC. Familial MTCs that have familial inheritance and are not associated with hyperparathyroidism and pheochromocytoma are now considered a variant of the MEN2A syndrome. Hereditary MTCs typically tend to be bilateral and multicentric. In MEN2A syndrome characterized by MTC, pheochromocytoma

and primary parathyroid hyperplasia, the penetrance of MTC is close to 100%. In MEN2B syndrome, on the other hand, the hereditary predisposition is in MTC and pheochromatisoma. Hyperparathyroidism is not seen. MTC is present in all patients and patients have a marfanoid appearance, mucosal neuromas, and intestinal ganglioneuromatosis. In hereditary MTC, they occur with thyroid nodules and/or cervical lymphadenopathies, just like sporadic cases. Screening and early diagnosis of family members at risk can be lifesaving. If germline RET mutation is detected in the index case, 1st and 2nd-degree family members are genetically screened. MEN2-related tumors are searched in individuals with mutations. Prophylactic surgical interventions are applied to carrier individuals who have not yet developed cancer.

The diagnosis of MTC is made by fine-needle aspiration biopsy (FNAB) taken from the nodule. The sensitivity of the technique is increased when calcitonin stain is applied immunohistochemically. In addition, calcitonin wash-out measurement from FNAB material may help the diagnosis. Measurement of serum calcitonin is not a routine method used to search thyroid nodules, since the specificity of measurement of serum calcitonin levels is not high. However, this can be examined in patients with clinical, radiological, and FNAB suspected MTC. Calcitonin can be found to be high in patients with hypercalcemia, hypergastrinemia, neuroendocrine tumors, kidney failure, papillary and follicular thyroid cancers, goiter, and autoimmune chronic thyroiditis, apart from MTC. In addition, people with high calcitonin heterophilic antibody levels may have high calcitonin levels. Long-term use of beta-blocker, omeprazole, and glucocorticoid is also associated with hypercalcitoninemia [5]. Although pentagastrin-stimulated calcitonin levels are routinely used for diagnosis in some European countries, they are not part of routine diagnostic practices in our country and in many countries around the world. CEA levels can also be high in the presence of inflammatory bowel diseases, benign lung diseases, and non-thyroid malignancies. Smoking habit can also increase CEA levels. Therefore, the diagnostic value of CEA is low, but it can be helpful in defining recurrences and relapses during follow-up.

Treatment in medullary thyroid cancer

Total thyroidectomy (TTx) is recommended in cases where neck lymph node metastasis or distant metastasis is not detected in the preoperative sonographic evaluation [6]. Lateral compartment dissection can be considered, based on basal Calcitonin (CT) values. Patients with cervical lymph node metastases should undergo central lymph node

dissection (CLND) together with TTx and dissection should be applied to the ipsilateral neck compartments. If the basal CT value is above 200 pg/mL, contralateral neck dissection can be performed in addition to ipsilateral lymph node dissection [6]. In the presence of distant metastasis, local-regional disease control should be achieved to prevent central neck morbidity, by performing less aggressive surgery that preserves the voice, airway and swallowing, and parathyroid functions.

In patients with diffuse distant metastases, palliative neck interventions may be necessary for the presence of pain or to provide a safe airway by opening the tracheal obstruction. Sometimes MTC can also be diagnosed after lobectomy. In such hereditary MTC, the other thyroid lobe should also be removed because, the risk of MTC development in the other thyroid lobe in the future is close to 100%. The rate of bilateral MTC is low in patients with sporadic MTC, there is not enough data on whether whether a completion thyroidectomy should be performed in this patient group. Among the low-grade patients who underwent lobectomy without considering sporadic MTC, complementary thyroidectomy and CLND are recommended for those with *RET* mutations, those with elevated postoperative serum CT, or those with imaging findings pointing to residual MTC.

Approach to Hereditary Cases or Carriers

Prophylactic thyroidectomy (PTx) should be administered to children in the highest risk category within the first year, even in the first months of their life. PTx should be administered to children in the high-risk category at the age of 5 years. CLND can be applied to children with a CT level above 40 pg/mL or those with lymph node metastases detected by imaging methods. By periodically following up children in the middle-risk category with PE, neck USG, and serum CT level measurements, thyroidectomies of these children can be postponed until after 5 years of age. TTx is recommended as early as possible in MEN 2B carriers, even if the CT level is 30-60 pg/mL. If the basal CT value is above 30-60 pg/mL, CLND should also be necessarily performed.

Postoperative Follow-up of MTC Cases

Since MTC is not a follicular neoplasm, TSH suppression is not required in the postoperative follow-up. However, LT4 replacement should be initiated in the early postoperative period to keep the patient at euthyroid levels. Patients should be followed up in terms of hypocalcemia. Generally, early postoperative transient hypocalcemias are observed, especially when CLND is performed. Oral calcium preparations and calcitriol

therapy should be initiated in patients with symptomatic hypocalcemia and persistent prolonged hypocalcemia. Follow-up differs significantly, depending on whether the case is familial or sporadic. The most important parameters in the postoperative follow-up of MTC patients are the TNM stage, lymph node metastases, and postoperative CT levels. Serum CT and CEA levels should be evaluated in the 3rd postoperative month. When CT values have not decreased postoperatively, if the causative focus can be localized and removed after a series of imaging methods, the patient can be operated on again. If localization studies are negative but basal and/or evoked CT levels are high, the patient is followed closely and a wait-and-see policy is applied.

Postoperative RAI treatment has no place in the treatment of MTC. In postoperative persistent disease, serial CT and CEA measurements and doubling times for these parameters can be calculated. CT doubling time is an important predictor for prognosis.

5-10-year survival rates for patients with a short doubling time (less than 6 months) are very low and aggressive treatment approaches are required for these patients. In low-risk patients with a doubling time longer than 2 years, follow-up can be continued with CT and CEA measurements every 6 months, a wait-and-see policy can be applied, and the survival time is long. Considering the 5- and 10-year survival rates in patients with a doubling time of 6 months to 2 years, additional treatment should be considered in these patients as well.

If the disease progresses or it is a case with no chance for surgery, tyrosine kinase inhibitors (TKIs) can be used within protocols. Palliative treatment modalities such as chemotherapy and RT may become a part of the process. In terms of MTC, follow-up and treatment in MEN 2 cases are not different from sporadic cases. Familial cases of MTC are families in which only MTC is observed for generations. However, since the mutations seen in these families are usually common with MEN 2A families, these families need to be followed for generations.

Metastatic MTC Treatment

Liver metastases are seen in 45% of advanced MTC cases. There are indications for treatment in large, enlarged, and symptomatic metastases. Surgical resection should be applied to isolated large hepatic metastases. Chemoembolization can be applied to diffuse metastatic lesions smaller than 30 mm and affecting less than 1/3 of the liver.

Lung metastases are usually multifocal and often together with mediastinal lymph

node metastases. Surgery should be applied to metastatic lesions that compress the airway and bleed. Radiofrequency ablation can be applied to peripheral and small metastases. Systemic treatments can be considered in the presence of multiple metastatic lesions that increase in size.

Vertebroplasty, surgical resection, thermoablation, cement injection, and RT are the therapy alternatives that can be applied in patients with bone metastases. If spinal cord compression is present, surgical decompression should be performed. If painful bone metastases are present, denosumab or bisphosphonate treatments are recommended. If neurological symptoms occur in metastatic MTC cases, brain imaging should necessarily be performed. Cutaneous metastases can also be seen rarely in MTC.

Systemic Treatment

In cases with persistent or recurrent MTC, single or combined cytotoxic chemotherapeutic treatment modalities are not recommended as a first-line treatment due to low response rates. The pathways associated with the activation of TKIs are effective in the development of MTC. Vascular endothelial growth factor receptors (VEGFR1 and VEGFR2) are frequently expressed in MTC, both in tumor cells and in the endothelium of vessels feeding the tumor. TKIs may be effective in the treatment of MTC by targeting and inactivating the kinase function of these receptors. Although significant reductions in tumor size are achieved with these treatments, complete remission or cure cannot be achieved. Currently, two FDA-approved TKIs with completed Phase 3 studies for MTC are vandetanib and cabozantinib.

Anaplastic Thyroid Cancer

Patients with anaplastic thyroid cancer (ATC) are usually over 60 years of age and they apply with clinical signs of a rapidly growing mass in the neck and local invasion of surrounding structures. Hoarseness, dysphagia, dyspnea, and pain are frequently encountered clinical symptoms. Regional lymph node involvement is common and lung metastases are present in approximately half of the patients at the time of diagnosis. Due to the rapidly progressive nature of this disease, its treatment is quite problematic.

It is also thought that ATC develops as a result of dedifferentiation of well-differentiated tumors and therefore RAI involvement is not observed. It is an aggressive tumor and it has a poor prognosis. Riedel's thyroiditis should also be considered in the

differential diagnosis. All anaplastic tumors, regardless of size, are classified as Stage IV disease. The majority of patients die from the local disease within months of diagnosis. Due to the tendency of the disease to invade the surrounding tissue locally, surgical intervention is not possible for most patients at the time of diagnosis. Thyroid Fine Needle Aspiration Biopsy (FNAB) may not be helpful in diagnosis and an open biopsy may be required. In most patients, surgical treatment is applied to prevent death due to airway obstruction and to provide airway. For this, partial thyroidectomies can be performed if necessary [7]. Aggressive surgery may be considered in rare selected cases with small-volume disease and no distant metastases. Very few patients have the opportunity to have thyroidectomy and complete resection performed. These patients show longer survival than patients who do not have the opportunity to have a thyroidectomy. ATC is insensitive to radiotherapy (RT), but combined regimens of chemotherapy and hyperfractionated RT show some benefit in terms of disease palliation. Doxorubicin is the most effective chemotherapeutic agent and shows a synergistic effect with RT. In these patients with an average life expectancy of less than 1 year, the longest survival was obtained in patients younger than 60 years of age, with diseases limited to the thyroid and who could undergo surgery [8].

Primary Thyroid Lymphoma

Primary thyroid lymphoma (PTL) is a rare disease usually seen on the basis of chronic thyroiditis. Although PTL is so rare, thyroid involvement can be detected in 10% of patients who die due to lymphoma. The frequency of PTL is increasing. Although the relationship of the disease with Hashimoto's thyroiditis is well known, the reason for this relationship can not be explained. The average age is around 62. They are often B-cell lymphomas. Some of them belong to the type of MALT lymphoma. Follicular lymphoma and Hodgkin lymphoma have also been reported rarely [9]. Thyroid lymphomas present as rapidly growing masses in the neck and may cause airway obstructions and difficulty in swallowing. It is most often confused with anaplastic cancer. A definitive diagnosis is made by open biopsy or coarse needle biopsy. In about half of the patients, the disease is localized to the thyroid, while in the other half involvement is present in the neck lymph nodes.

Radiotherapy (RT), chemotherapy, and surgery can be used in the treatment. Surgery can usually be used for diagnostic purposes or to open the airway and relieve pressure. In the presence of localized disease in the neck, surgery and/or radiotherapy are applied. Postoperative RT or chemotherapy is combined. Chemotherapy can be used in relapse cases.

Chemotherapy regimens usually include cyclophosphamide, adriamycin, vincristine, and prednisolone. It is also seen that it reduces recurrences when combined with RT. However, in case of local or distant relapse, survival does not change much with chemotherapy. Rituximab has also been reported to be used successfully in treatment [10].

RESOURCES

1. Wells SA Jr, Asa SL, Dralle H, et al. Revised American Thyroid Association guidelines for the management of medullary thyroid carcinoma. Thyroid 2015; 25:567.
2. Gagel RF, Hoff AO, Cote GJ. Medullary thyroid carcinoma. In: Werner & Ingbar's The Thyroid, 9th, Braverman LE, Utiger RD (Eds), Lippincott Williams & Wilkins, Philadelphia 2005. p.967.
3. Pacini F, Castagna MG, Cipri C, Schlumberger M. Medullary thyroid carcinoma. Clin Oncol (R Coll Radiol) 2010; 22:475.
4. Kwon H, Kim WG, Sung TY, et al. Changing trends in the clinicopathological features and clinical outcomes of medullary thyroid carcinoma. J Surg Oncol 2016; 113:152.
5. Yang JH, Lindsey SC, Camacho CP, et al. Integration of a postoperative calcitonin measurement into an anatomical staging system improves initial risk stratification in medullary thyroid cancer. Clin Endocrinol. 2015; 83:938.
6. Wells SA Jr , Asa SL, Dralle H, et al. Revised American Thyroid Association guidelines for the management of medullary thyroid carcinoma. Thyroid. 2015 Jun;25(6):567-610.
7. Smallridge RC, Ain KB, Asa SL, et al American Thyroid Association guidelines for management of patients with anaplastic thyroid cancer.. Thyroid. 2012;22(11):1104-39.
8. Ito K, Hanamura T, Murayama K, et al. Multimodality therapeutic outcomes in anaplastic thyroid carcinoma: improved survival in subgroups of patients with localized primary tumors. Head Neck 2012; 34:230.
9. Katna R, Shet T, Sengar M, et al. Clinicopathologic study and outcome analysis of thyroid lymphomas: experience from a tertiary cancer center. Head Neck 2013; 35:165.
10. Cha H, Kim JW, Suh CO, et al. Patterns of care and treatment outcomes for primary thyroid lymphoma: a single institution study. Radiat Oncol J 2013; 31:177.

2.6. Bladder Cancer

Epidemiology:

Bladder cancer is the second most common cancer of the genitourinary system. Bladder cancer is the 10th most common cancer type in the world, with an estimated 549,000

new cases and 200,000 deaths. Bladder cancer is more common in men than women, with incidence and mortality rates being 9.6 per 100,000 in men and 3.2 in women. Therefore, it is the sixth most common cancer among men and ninth in terms of mortality among men [1]. According to geographical distribution, bladder cancer has a high incidence in Western Europe and North America, while low incidence rates are present in Asia and Eastern Europe [2]. According to the 2016 statistics of the Ministry of Health, Public Health Directorate, 22,612 cases were detected between 2012 and 2016 in our country, and bladder cancer is the fourth most common cancer seen among men. In women, on the other hand, bladder cancer is not among the top ten most common cancers [3]. Bladder cancer is typically diagnosed more often in the elderly. The median age is 69 in men and 71 in women [4].

Risk Factors

Chemical carcinogenesis, which occurs as a result of exposure to environmental carcinogens, plays an important role in the formation of bladder cancer. Tobacco products, including cigarettes, are the most important environmental factor contributing to the incidence of bladder cancer. Smokers have a lower age at diagnosis and the risk is higher by an average of 4 times, compared to non-smokers[5]. There are more than 60 known carcinogens in cigarettes. Studies have shown that bladder tumors with higher grade and muscle invasion are seen in smokers who smoke more than 30 packs/year, compared to non-smokers [6]. Even quitting smoking has been shown to reduce the recurrence rate after diagnosis [7].

Apart from smoking, exposure to occupational and environmental chemical components also causes the development of bladder cancer. Especially metal workers, rubber industry, leather, textile and electrical workers, miners, cement and transport workers, carpet manufacturers and painters have been associated with an increased risk of cancer due to various dyes, plastics and chemicals [8,9]. The use of some herbal products containing arsenic and aristolochic acid also leads to an increase in the risk of bladder cancer [10].

Chronic and recurrent bladder infections, human papillomavirus infections (HPV), and infestations seen in Africa and the Middle East related to the freshwater parasite Schistosoma Hematobium are also associated with an increased risk of bladder cancer [11]. Cyclophosphamide and ifosfamide, which are alkylating chemotherapy agents used in the treatment of many different types of cancer, are also associated with an increased risk of bladder cancer. Acrolein, which is a metabolite of cyclophosphamide, has been shown to

cause both bleeding bladder infection and bladder cancer [12].

The use of pain reliever *Phenacetin*, which was widely used until the end of the 1980s, was also discontinued, as it increased the risk of bladder cancer. The relationship between the Pioglitazone drug used in the treatment of Type 2 Diabetes Mellitus and bladder cancer has been found to be contradictory in many studies done previously. Therefore, it should be used with caution, especially in patients at risk.

Many epidemiological and clinical studies have shown that genetic susceptibility plays an important role in the development of bladder cancer, along with environmental exposure. Carcinogenesis emerges as a result of a complex process with external exposures and family history as aresult of complex interactions of oncogenes, tumor suppressor genes, various growth factors and receptors.

Clinic, Diagnosis and Staging

At the time of diagnosis, approximately 75% of bladder tumors are limited to the superficial bladder mucosa and they are defined as superficial bladder cancer. The remainder has invaded the bladder muscle layer and it is called invasive bladder cancer [13]. The most common symptom in bladder cancer is hematuria, which is usually intermittent, coarse, painless, and present throughout micturition. Although hematuria is present in many different benign diseases, it requires further investigation due to the suspicion of bladder cancer in asymptomatic cases of unknown origin, especially at advanced ages. Side pain due to the tumor causing ureteral obstruction, bladder outlet obstruction and suprapubic and/or pelvic pain due to the spread of the tumor to surrounding tissues, diffuse body pain due to the abdominal organ or bone metastases may be seen. In addition, intermittent, frequent, burning, irritative urination findings are also encountered. In advanced stages, weakness, weight loss, renal failure due to bilateral urinary obstruction can be seen. On physical examination of advanced patients, pelvic or abdominal masses and inguinal region lymph nodes may be palpable.

Patients presenting with unexplained hematuria should undergo a complete urological evaluation to rule out other benign causes and renal pathologies. Cystoscopy, which is performed after a complete urine test done with microscopic examination and dipstick chemical test, is the gold standard method in the initial diagnosis and staging. With

this method, which is performed with a flexible cystoscope and has minimal risk in terms of bleeding and infection, both the inside of the bladder is visualized, transurethral tumor resection (TUR) is performed, and the tumor is taken for definitive pathological diagnosis and staging (whether there is muscle invasion), and the initial treatment of the tumor is completed with resection.

Imaging the urinary system is recommended in all cases, regardless of stage. Pelvic and abdominal computed tomography (CT) is generally the method of choice [14]. Magnetic resonance imaging (MRI) is as reliable as CT for staging invasive or locally advanced disease and may be better at evaluating tumors at the base and dome of the bladder. Since the risk of metastasis is high in locally advanced patients, abdominal and thoracic CT are frequently used to detect possible distant metastases. Radionuclide scanning scintigraphies for bone lesions should be considered in patients with unexplained elevated serum alkaline phosphatase or symptomatic pain. Suspicious cases are confirmed with pathology by performing CT, MRI, or biopsy, when necessary.

The stage of the disease is the most important independent prognostic factor for progression-free and overall survival. The eighth edition (2017) of the tumor, node, metastasis (TNM) system is used for staging. The important prognostic determinant in staging is whether the tumor is limited to the bladder (≤T2) or whether it has extra-bladder involvement (≥T3). In the case of extensive metastases such as lung, liver, and bone, there is no chance of curative treatment and the long-term prognoses of the patients are poor.

Treatment

TUR operation is the main treatment for superficial bladder cancers without muscle invasion. In some patients with low-grade tumors, two or more resections may be required to remove all visible lesions. Perioperative single dose intravesical chemotherapy (usually with mitomycin C) may be given to patients with low-grade tumors. In patients with high-risk superficial bladder cancer, control cystoscopy is definitely performed and resection is performed when necessary, due to the risk of residual and recurrence. For 6 weeks after TUR, Weekly intravesical Bacillus Calmette-Guerin (BCG) therapy is indicated in patients with moderate and high-risk disease, and the patient is usually followed up with maintenance therapy.

In the case of bladder cancer with muscle invasion or superficial cancers unresponsive to TUR and intravesical treatments, the method of choice is radical cystectomy and urinary diversion [14]. In randomized controlled clinical studies related to muscle-invasive bladder cancer, preoperative neoadjuvant platinum-based chemotherapy has been shown to provide a survival advantage; therefore, it is applied as a standard in medically fit patients. In patients who are operated without neoadjuvant therapy, adjuvant therapy is usually given, but the effectiveness of adjuvant therapy has not been proven as well as neoadjuvant therapy.

In muscle-invasive bladder cancer, for patients who are not suitable for surgery or refuse to be operated on, chemo-radiotherapy given simultaneously after TUR is the main treatment option. There are no randomized comparative efficacy studies related to surgery and curative chemo-radiotherapy. In cases that relapse after chemoradiotherapy, radical cystectomy is recommended, if possible.

After treatment, patients are carefully followed in terms of the risk of relapse. It is checked every 3 months in the first year, every 6 months in the second and third years, then annually with urine cytology, liver and kidney function tests, and electrolytes. Follow-up with CT imaging (chest, abdomen, and pelvis) is recommended at 6 months for the first three years, then annually until the fifth year.

Systemic treatment is the method that prolongs survival in advanced metastatic disease with no cure chance. Platinum-based chemotherapies are the primary treatments of choice. Despite response being achieved to multiple platinum-based regimens, disease progression is inevitable. In recent years, with the rapid introduction of immunotherapy agents that trigger the immune system against cancer cells into oncology practice, immunotherapy has become the preferred approach for metastatic bladder cancer patients who have progressed during or after chemotherapy. Longer survival advantages can be achieved with drugs with proven effectiveness and approval for use, such as Pembrolizumab, Nivolumab, Atezolizumab. In advanced bladder cancer, many promising studies are ongoing, especially with targeted molecule FGFR inhibitors (such as erdafitinib).

RESOURCES

1. Bray F, Ferlay J, Soerjomataram I, et al. Global CancerStatistics 2018: GLOBOCAN

Estimates of IncidenceandMortalityWorldwidefor 36 Cancers in 185 CountriesCaCancer J Clın 2018;68:394–424

2. Pelucchi C, Bosetti C, Negri E et al. Mechanisms of disease: Theepidemiology of bladdercancer. NatClinPractUrol. 2006;3(6):327.
3. T.R. Ministry of Health General Directorate of Public Health 2016 Turkey Cancer Statistics Ankara 2019
4. Lynch CF, Cohen MB Urinarysystem. Cancer. 1995;75(1 Suppl):316.
5. Freedman ND, Abnet CC, Caporaso NE et al. Impact of changing US cigarettesmokingpatterns on incidentcancer: risks of 20 smoking-relatedcancersamongthewomenand men of the NIH-AARP cohort. Int J Epidemiol. 2016;45(3):846.
6. Pietzak EJ, Mucksavage P, Guzzo TJ, Malkowicz SB Heavy Cigarette Smokingand Aggressive Bladder Cancer at Initial Presentation. Urology. 2015;86(5):968.
7. Chen CH, Shun CT, Huang KH et al. Stopping smoking mightreducetumourrecurrence in nonmuscle-invasivebladder cancer. BJU Int. 2007;100(2):281.
8. Kogevinas M, 't Mannetje A, Cordier S et al. Occupation and bladder cancer among men in Western Europe. CancerCauses Control. 2003;14(10):907.
9. Smailyte G, Kurtinaitis J, Andersen A
10. Mortality and cancer incidence among Lithuanian cement producing workers.Occup Environ Med. 2004;61(6):529.
11. Lai MN, Wang SM, ChenPC Population-basedcase-controlstudy of Chinese her balproduc tscontainingaristolochicacidandur inarytract cancer risk. J NatlCancerInst. 2010;102(3):179. Epub 2009 Dec 21.
12. Mostafa MH, Sheweita SA, O'ConnorPJ Relationship betweensc histosomiasis and bladder cancer. Clin Microbiol Rev. 1999;12(1):97.
13. Pedersen-Bjergaard J, Ersbøll J, HansenVL Carcinoma of theurinary bladder after treatment with cyclophosphamidefornon-Hodgkin'slymphoma.
14. N Engl J Med. 1988;318(16):1028.
15. JemalA, Bray F, Melissa M. Global Cancer Statistics Ca Cancer J Clın 2011;61:6990
16. Chang SS, Bochner BH, Chou R et al. Treatment of Non-MetastaticMuscle-Invasive Bladder Cancer: AUA/ASCO/ASTRO/SUO Guideline. J Urol. 2017;198(3):552. Epub 2017 Apr 26.

2.7. Gastric Cancer

Gastric cancer is a disease that originates from the gastric mucosal epithelium, spreads into the lumen and/or intramural, has a multifactorial etiology, and is seen commonly in the

world. With respect to location, the tumor is localized with a rate of 30% in antrum, 30% corpus, 30% fundus-cardia and 10% diffusely (1,2).

In recent years, there has been a gradual decrease in gastric cancer rates in many populations. However, not all types of gastric cancer are declining: tumors of the cardia and esophagogastric compund are occurring with increasing frequency. An unexplained increase in the incidence of gastric cancer among persons under 40 years of age has been reported [3].

Most patients with gastric cancer are symptomatic and have advanced disease at admission. However, despite advances in medicine, metastases are detected in approximately 50 percent of patients at admission, and only half of those without metastatic tumors have a chance of curative resection [4].

Epidemiology

According to the global cancer research GLOBOCAN data, gastric cancer is the fifth most common cancer type in the world and the third among cancer-related deaths. 5.7% of all cancer cases diagnosed in 2018 are gastric cancer. 8.2% of cancer-related deaths are due to gastric cancer. The geographical distribution of gastric cancer differs by region. According to the cancer prevalences of the last 5 years, 76.4% of the cases were reported from the Asian region, 12.3% from the European region, and 5.6% from the Latin America and Caribbean region. Men are more disadvantaged compared to women in terms of the development of gastric cancer. The global age-standardized gastric cancer rate is found to be 7.0 for women and 15.7 for men per population of 100,000 [5].

It has been shown that socioeconomic status and ethnicity are associated with the anatomical region where cancer originates. In a study conducted with the data of the American National Cancer Institute, 77,881 gastric cancer cases were examined and individuals who developed cardia type gastric cancer were found to be more likely to belong to the non-Hispanic white group. On the other hand, it has been shown that individuals who develop noncardia-type gastric cancer are often from Hispanic groups, and if they are from non-Hispanic groups, they are among black, Asian and Pacific Islander, Indian-American, and Alaska-born individuals [6].

Gastric cancer is the 5th most common cancer type in Turkey in terms of new case incidence. According to mortality rates, it is the second most common type of cancer that

causes death. In Turkey, 8.6% of cancer deaths occurred due to gastric cancer in 2018 [7].

Etio-Pathogenesis

Many factors related to the environment and host are effective in the etiology of gastric cancer. 75-90% of gastric cancers belong to the H.pylori-associated noncardiac type. Factors such as living in a crowded environment and low socioeconomic level lead to the development of this type of cancer. The recent decrease in the frequency of noncardiac type gastric cancer is explained by the reasons such as improved food storage conditions and better nutrition opportunities. Cardiac gastric cancers, whose frequency is increasing, are generally associated with a sedentary lifestyle, obesity, and overweight [8].

"H. pylori infection, tobacco use, exposure to X and γ-ray and working in the rubber manufacturing industry" has been listed as a class 1 cancer factors for gastric cancer, by the International Agency for Research on Cancer- IARC. Exposure to asbestos, Ebstein Barr Virus infection, leaded compounds, oral intake of inorganic nitrates and nitrites, consumption of pickled vegetables, processed meat, and salty food are the environmental factors that are accused in the etiology [9].

Nitrate compounds and polycyclic aromatic hydrocarbons, which are accused of cancer formation, are formed during red meat cooking and smoking processes. In addition, low intake of fresh fruits and vegetables and alcohol use are also listed among behavioral risk factors [10].

Many genetic factors play a role in the etiology of gastric cancer. One of the most important factors is the E-cadherin gene mutation. This mutation leads to diffuse type gastric cancer [11]. In the pathogenesis of an average of 30-40% of hereditary diffuse cancers, CDH1 germline E-Cadherin mutation is seen. In addition, the presence of genes such as TP-53, HER2, CD44, ERB B2 was found to be effective in diagnosis, prognosis and response to treatment. The presence of Cag A (Cytotoxin-related gene) has diagnostic importance in H. pylori-associated gastric cancer types [12].

Rare causes of hereditary gastric cancer include Lynch syndrome, FAP, Li-Fraumeni syndrome, Peutz-Jeghers syndrome, Juvenile polyposis and Cowden syndrome [13].

The risk of gastric cancer increases after gastric surgery: the Billroth II procedure

(gastrojejunostomy) carries a higher risk than the Billroth I procedure (gastroduodenostomy). Although the exact cause of the increased risk is unknown, it is thought to be due to insufficiency of bile and pancreatic secretion (more effective after the Billroth II procedure, compared to after the Billroth I procedure) [13].

Cancer begins in situ from the gastric mucosal epithelium and deepens gradually. Atrophy/hyperplasia, metaplasia, dysplasia and eventual cancer cell occur. Recently, it is thought that stem cells play a central role in the development of gastric cancer and the tumor-derived from stem cells originating from the stomach and/or bone marrow (13,14).

Prognosis

The factors determining the prognosis are the T stage of the tumor, N stage, presence of cancer-related complications (perforation, stenosis, hemorrhage), cell type of the tumor, and histological differentiation. The most important factor affecting the prognosis is the stage of the disease (1, 2, 15).

The five-year survival rate reaches 90% in Japan, which can be said to be relatively good compared to other regions. This rate varies between ~10% and 30% in European countries. The high survival rate in Japan is probably provided by early diagnosis with endoscopic examinations and consecutive early tumor resection (16,17). Survival rates are similar between patients who undergo endoscopic resection and patients who undergo surgical resection (94% and 96%, respectively) (18).

The postoperative recurrence rates are approximately 1 to 5 percent in reports from Korea and Japan, and 5 to 15 percent in studies from Western centers (19,20). It has been reported that the recurrence rate in patients undergoing endoscopic resection is between 0 and 30 percent (21).

Classification

Borrmann and Lauren classifications are used for the definition of gastric cancer.

Borrmann classification is based on macroscopic appearance and tumors are classified into four different types: Type1, polypoid tumors; Type 2, limited collapsed tumors; Type 3, ulcerated tumors and Type 4, diffuse infiltrating tumors. Early gastric cancer (EGC) is absent in the original Borrmann classification, but it has been classified as type 0 in the Japanese gastric cancer classification in recent years. The Japanese classification

divides EGC into three types: Type I (protruded type), Type II (superficial type), and Type III (excavated type) (22).

The Lauren classification is also a frequently used classification, and according to this classification, gastric tumors are divided into intestinal and diffuse types. Intestinal type chronic atrophic gastritis may develop from a series of precursor lesions such as chronic atrophic gastritis, dysplasia and invasive carcinoma (atrophy metaplasia, dysplasia, carcinoma lineage), together with intestinal metaplasia, whereas diffuse gastric carcinomas such as signet ring cell carcinoma develop independently of intestinal metaplasia (23).

Diffuse type gastric cancers are cancers with more metastatic features, which have rapid progression and poor prognosis. It invades the stomach wall more, sometimes invades the distal esophagus and duodenum, and sometimes causes linitis plastic. Like intestinal cancers, it can be induced by H. pylori. Somatic mutations in the E-cadherin gene are found in sporadic diffuse gastric cancer at a frequency of 40–83% [14].

Intestinal type gastric cancer is the most common type in high-risk populations. It shows sporadic features with higher probability. H. pylori is associated with environmental factors such as diet, smoking, and alcohol use. In addition, it is the type that has decreased most markedly in recent years (24,25).

Rare types of gastric cancer arising from the stroma and mesenchyme of the stomach:

Gastrointestinal stromal tumors (GIST): These neoplasms are mostly found in the stomach and proximal small intestine, but they can occur in any part of the digestive tract, sometimes in the omentum, mesentery, and peritoneum. GISTs often contain activating mutations in KIT or platelet-derived growth factor receptor alpha (*PDGFRA)* genes (26).

Gastric lymphomas: They constitute less than 5% of gastric neoplasms. Non-Hodgkin lymphoma is mostly seen in the stomach, except for the lymph nodes. The macroscopic appearance may be polypoid, ulcerative, or infiltrative. Diagnosis is made with endoscopic biopsy. It is known that MALT-type lymphomas are closely related to H. pylori. In some of these patients, the cure is achieved with H. pylori eradication therapy (27).

Gastric sarcomas: They cover 13% of malignant tumors of the stomach. The most common is leiomyosarcoma, and less frequently angiosarcoma, fibrosarcoma, and liposarcoma are seen (26).

Gastric carcinoids: This very rare tumor arises from enterochromaffin cells in the gastrointestinal tract. 3% of all carcinoid tumors are located in the stomach. Symptoms such as hot flushes, palpitations, diarrhea, pain, and nausea may occur due to serotonin and histamine secretion. All carcinoids are potentially malignant and may metastasize (26).

Symptoms and findings

Most patients are symptomatic at the time of admission. Weight loss and persistent abdominal pain are the most common symptoms in the initial diagnosis (Table-5). There is no specific symptomatology. Approximately 25 percent of patients have a history of gastric ulcers (28).

Patients may also present with symptoms of distant metastatic diseases. The most common sites of metastasis are the liver, peritoneal surfaces, and non-regional or distant lymph nodes. Less commonly, the ovaries, central nervous system, bone, lung, and soft tissue metastases occur.

In patients with lymphatic invasion, physical examination may present with left supraclavicular lymph node (Virchow nodule) (the most common physical examination finding of metastatic disease), a periumbilical nodule (Sister Mary Joseph nodule), left axillary lymph node (Irish nodule), ovarian tumor (Krukenberg) or a mass (Blummer's shelf) on rectal examination (29-32).

Ascites may be the first sign of peritoneal carcinomatosis. If jaundice or any sign of liver failure is observed, the advanced metastatic disease should be considered. In addition, microangiopathic hemolytic anemia, membranous nephropathy and hypercoagulation conditions (Trousseau syndrome) may be seen due to complications (perforation, obstruction, hemorrhage) and paraneoplastic symptoms. As with most advanced gastrointestinal malignancies, in gastric cancer patients, pulmonary embolism may develop into Polyarthritis nodosa. Acanthosis nigricans (axillary and perineal discoloration) and peripheral neuropathy may be observed (33).

Table 5. Presenting Symptoms of 18.363 Gastric Cancer Patients (28)

Symptom	Frequency (%)
Weight loss	62
Stomach ache	52
Nausea	34
Difficulty in swallowing	26
Melena	20
Early satiety	18
Ulcer-like ache	17

Diagnosis

The definitive diagnosis of gastric cancer is made pathologically by taking a biopsy together with endoscopy, endoscopic ultrasonography (EUS), and computed tomography (CT) (34). The reported accuracy of white light endoscopy for EGC detection ranges from 90 to 96 percent, but in some studies lower values have been found (35). On endoscopy, EGC can be seen as a thin polypoid protrusion, a superficial plaque, mucosal discoloration, or ulcer (36).

Gastric ulcer that appears suspicious during endoscopy should be **biopsied**. As up to 5 percent of malignant ulcers appear benign, it is required to histologically evaluate all these lesions with biopsy. A single biopsy has a 70 percent sensitivity for diagnosing gastric cancer, whereas taking seven biopsy samples from the edge and base of the ulcer raises the sensitivity to over 98 percent (37).

Serum levels of the serum tumor markers CEA, CA 125, CA 19-9 and CA 72-4 may be elevated in patients with gastric cancer. The low sensitivity and specificity rates prevent the use of any of these serological markers as diagnostic tests for gastric cancer. Serum tumor markers provide limited benefit in selected patients (38).

Tumor spread in patients with pathologically diagnosed cancer is evaluated with Positron Emission Tomography (PET-CT). With the widespread use of endoscopy, the frequency of early diagnosis of gastric cancer is increasing (34).

Protection and Screening

The recent decrease in the frequency of gastric cancer is attributed to the provision of sanitation facilities, the widespread use of refrigerators, the improvement of food storage conditions and the use of antibiotics that effectively eradicate H.pylori infection (39). From this point of view, strategies for cancer prevention are based on eliminating H. pylori infection, increasing daily intake of fresh fruits and vegetables and increasing physical activity, reducing salt consumption, obesity, and tobacco use. The risk of cancer increases in patients with extensive atrophic or metaplastic changes in the gastric mucosa. Periodic endoscopic surveillance is recommended in these patients (40). This type of surveillance is necessary if incomplete metaplasia or dysplasia is recognized. Endoscopic resection is a viable strategy if the lesions are clearly defined topographically. In Japan, with endoscopic resection of such lesions, 5-year survival rises to 90% (41).

Upper gastrointestinal radiography has been used for screening in Japan, but gastroscopy is the most useful tool for detecting EGC. In high-risk populations (with a family history of gastric cancer, immigrants from high-incidence areas, patients with known gastric atrophy, intestinal metaplasia, or dysplasia), gastric topographic biopsy mapping should be considered (42,43).

Treatment

The treatment method in gastric cancer is determined on the basis of TNM staging; Stage I: Early-stage gastric cancer (<2 cm), Stage II, III: Locally Advanced gastric cancer, and Stage IV: Metastatic gastric cancer (2,44). The main treatment for gastric cancer is surgery. Surgery consists of two stages, which are resection and reconstruction. However, in early-stage gastric cancer, endoscopic resection (ER) is an endoscopic alternative to surgical resection of mucosal and submucosal neoplastic lesions and intramucosal cancers. ER includes endoscopic mucosal resection (EMR), which includes snare resection of dysplastic lesions, and endoscopic submucosal dissection (ESD), in which endoscopic tools are used to examine submucosal lesions. ER offers both diagnosis and treatment

(45,46). EMR and ESD should be performed by experienced endoscopists (47). In locally advanced cancer, preoperative (neoadjuvant) and postoperative (adjuvant) chemoradiotherapy and biological therapy (smart drug) can be added. The main purpose of neoadjuvant therapy is to make the tumoral tissue resectable surgically (48).

Depending on the localization of the tumor, both subtotal and total gastrectomy are used. Total gastrectomy is performed for lesions located in the upper 1/3 of the stomach, whereas subtotal gastrectomy is performed for lesions located in the lower 2/3 of the stomach. Positive results have been reported with pylorus-preserving gastrectomy in patients with EGC in the middle 1/3 of the stomach (49,50). While open gastrectomy remains the standard surgical treatment for gastric cancer worldwide, laparoscopic gastrectomy is performed with increasing frequency in high-volume centers. Laparoscopic gastric cancer surgery is most often performed for early gastric cancers that are not suitable for endoscopic resection. In unresectable cases palliative treatments are applied for complications (4,48,51,52).

RESOURCES

1. Dharmarajan S, Halpin VJ, Hawkins WG. Stomach. The Washington Manual of Surgery.5th Edition. Washington, 2008;168-80.
2. Zinner MJ, Ashley SW. Maingots Abdominal Operations. 12th ed. London, 2013:463-89.
3. Anderson WF, Camargo MC, Fraumeni JF Jr, et al. Age-specific trends in incidence of noncardia gastric cancer in US adults. JAMA. 2010; 303:1723–8.
4. Internet: Mansfield F Paul. Surgical management of invasive gastric cancer. UpToDate Access: 05.20.2020.
5. Internet: https://gco.iarc.fr/today/data/factsheets/cancers/7-Stomach-fact-sheet.pdf Erişim: 19.05.2020.
6. Gupta, Samir, et al. Race/ethnicity-, socioeconomic status-, and anatomic subsite-specific risks for gastric cancer. Gastroenterology, 2019, 156.1: 59-62. e4.
7. Internet: https://gco.iarc.fr/today/data/factsheets/populations/792-turkey-fact-sheets.pdf Erişim: 19.05.2020.
8. Arnold, Melina, et al. "Recent trends in incidence of five common cancers in 26 European countries since 1988: Analysis of the European Cancer Observatory." *European journal of cancer* 51.9 (2015): 1164 1187.https://doi.org/10.1016/j.ejca.2013.09. 002
9. Internet: https: //monographs. iarc. fr/wpcontent/uploads/2019/07/ Classifications _by_cancer_site.pdf Access: 05.20.2020

10. IARC (2012). Biological agents. IARC Monogr Eval Carcinog Risks Hum. 100B:1–441. Available from: http://publi cations.iarc.fr/119
11. Cristescu, R., Lee, J., Nebozhyn, M. *et al.* Molecular analysis of gastric cancer identifies subtypes associated with distinct clinical outcomes. *Nat Med* 21, 449–456 (2015). https://doi.org/10.1038/nm.3850
12. Wild CP, Weiderpass E, Stewart BW, editors (2020). World Cancer Report: Cancer Research for Cancer Prevention. Lyon, France: International Agency for Research on Cancer. Available from: http://publications.iarc.fr/586.
13. Annie On On Chan, et al. Risk factors for gastric cancer. UpToDate 17 May 2020.
14. Internet: Richard M Goldberg, et al. Pathology and molecular pathogenesis of gastric cancer. UpToDate. Access: 05.17.2020.
15. Gu L, Chen M, Guo D, Zhu H, Zhang W, Pan J, et al. PD-L1 and gastric cancer prognosis: A systematic review and meta-analysis. PLoS One. 2017;12(8):e0182692.
16. Stock M, Otto F. Gene deregulation in gastric cancer. *Gene*. 2005;360(1): 1–19.
17. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics 2002. *CA Cancer J Clin*. 2005;55(2):74–108.
18. Pyo JH, Lee H, Min BH, et al. Long-Term Outcome of Endoscopic Resection vs. Surgery for Early Gastric Cancer: A Non-inferiority-Matched Cohort Study. Am J Gastroenterol 2016; 111:240.
19. Choi IJ, Lee JH, Kim YI, et al. Long-term outcome comparison of endoscopic resection and surgery in early gastric cancer meeting the absolute indication for endoscopic resection. Gastrointest Endosc 2015; 81:333.
20. Hiki Y, Shimao H, Mieno H, et al. Modified treatment of early gastric cancer: evaluation of endoscopic treatment of early gastric cancers with respect to treatment indication groups. World J Surg 1995; 19:517.
21. Abe S, Oda I, Suzuki H, et al. Short- and long-term outcomes of endoscopic submucosal dissection for undifferentiated early gastric cancer. Endoscopy 2013; 45:703.
22. Japanese Gastric Cancer Association. Japanese classification of gastric carcinoma, 2nd English edition. Gastric Cancer 1998; 1: 10-24.
23. Carneiro F, Huntsman DG, Smyrk TC, et al. Model of the early development of diffuse gastric cancer in E-cadherin mutation carriers and its implications for patient screening. J Pathol 2004; 203: 681-7.
24. Henson DE, Dittus C, Younes M, et al. Differential trends in the intestinal and diffuse types of gastric carcinoma in the United States, 1973-2000: increase in the signet ring cell type. Arch Pathol Lab Med 2004; 128:765.

25. Locke GR 3rd, Talley NJ, Carpenter HA, et al. Changes in the site- and histology-specific incidence of gastric cancer during a 50-year period. Gastroenterology 1995; 109:1750.
26. internet: Morgan jeffrey, et al. Local treatment for gastrointestinal stromal tumors, leiomyomas, and leiomyosarcomas of the gastrointestinal tract. UpToDate Access: 05.23.2020.
27. Internet: S freedman arnold, et al. Treatment of extranodal marginal zone lymphoma of mucosa associated lymphoid tissue (MALT lymphoma). UpToDate Access: 05.23.2020.
28. Wanebo HJ, Kennedy BJ, Chmiel J, et al. Cancer of the stomach. A patient care study by the American College of Surgeons. Ann Surg 1993; 218:583.
29. Morgenstern L. The Virchow-Troisier node: a historical note. Am J Surg 1979; 138:703.
30. Pieslor PC, Hefter LG. Umbilical metastasis from prostatic carcinoma--Sister Joseph nodule.Urology 1986; 27:558.
31. Gilliland R, Gill PJ. Incidence and prognosis of Krukenberg tumour in Northern Ireland. Br J Surg 1992; 79:1364.
32. Winne BURCHARD BE. Blumer's shelf tumor with primary carcinoma of the lung. A case report. J Int Coll Surg 1965; 44:477.
33. Fuchs CS, Mayer RJ. Gastric carcinoma. N Engl J Med 1995; 333:32.
34. Gao LM. The book of Gastric Cancer: Diagnosis and treatment of gastric cancer. Transl Gastroenterol Hepatol. 2016;1:54.
35. Ballantyne KC, Morris DL, Jones JA, et al. Accuracy of identification of early gastric cancer. Br J Surg 1987; 74:618.
36. Kajitani T. The general rules for the gastric cancer study in surgery and pathology. Part I. Clinical classification. Jpn J Surg 1981; 11:127.
37. Graham DY, Schwartz JT, Cain GD, Gyorkey F. Prospective evaluation of biopsy number in the diagnosis of esophageal and gastric carcinoma. Gastroenterology. 1982; 82: 228.
38. Marrelli D, Pinto E, De Stefano A, et al. Clinical utility of CEA,CA 19-9, and CA 72-4 in the follow-up of patients with resectable gastric cancer. Ben J Surg 2001; 181: 16.
39. Crew, K. D., Neugut, A. I. Epidemiology of gastric cancer. World journal of gastroenterology: WJG, 2006, 12.3: 354. https://doi.org/10.3748/wjg.v12.i3.354
40. Correa P, Piazuelo MB, Wilson KT. Pathology of gastric intestinal metaplasia: clinical implications. Am J Gastroenterol. 2010; 105:493–8.
41. Miyahara R, Niwa Y, Matsuura T, et al. Prevalence and prognosis of gastric cancer detected by screening in a large Japanese population: data from a single institute over 30 years. J Gastroenterol Hepatol. 2007; 22:1435–42.

42. Kim GH, Liang PS, Bang SJ, Hwang JH. Screening and surveillance for gastric cancer in theUnited States: Is it needed? Gastrointest Endosc 2016; 84:18.
43. Taylor VM, Ko LK, Hwang JH, et al. Gastric cancer in asian american populations: a neglected health disparity. Asian Pac J Cancer Prev 2014; 15:10565.
44. Ergüney S, Yavuz N. Neoplasm of Stomach Basic Surgical Fourth Edition. Ankara, 2010; 1277- 92.
45. Sydiuk A. Current practice for gastric cancer treatment in Ukraine. Transl Gastroenterol Hepatol. 2017;2:47.
46. Internet: Gunaratnam T Naresh, et al. Overview of endoscopic resection of gastrointestinal tumors. UpToDate Access: 05.20.2020.
47. Şenateş E, İnce Aİ. Early Gastric Cancer Current Gastroenterology. 2011;15(3):161-66.
48. Kumagai K. Current Status and Future Views of Gastric Cancer Treatment in Elderly Patients. Gan To Kagaku Ryoho. 2016;43(9):1058-62.
49. Folli S, Dente M, Dell'Amore D, et al. Early gastric cancer: prognostic factors in 223 patients. Br J Surg 1995; 82: 952-6.
50. Morita S, Katai H, Saka M, et al. Outcome of pylorus-preserving gastrectomy for early gastric cancer. Br J Surg 2008; 95: 1131-5.
51. Lazăr DC, Tăban S, Cornianu M, Faur A. New advances in targeted gastric cancer treatment. World J Gastroenterol. 2016;22(30):6776-99.
52. Japanese Gastric Cancer Association. Japanese gastric cancer treatment guidelines 2014 (ver. 4). Gastric Cancer. 2017 ;20 (1):1-19.

2.8. Uterine Corpus

Uterine malignancies are analyzed in two categories: endometrial cancers arising from the hormone-sensitive gland epithelium and sarcomas arising from the stroma. Endometrial cancer is the most common gynecological malignancy and is also called uterine cancer. [1]Sarcomas, on the other hand, constitute less than 3% of all uterine malignancies, and their treatment and prognosis are completely different from endometrial cancer [2].

Risk Factors

1. Increased oestrogen levels (obesity, Diabetes and fatty diet),
2. Early menarche,
3. Late menopause,
4. Lynch syndrome,

5. Advanced age (≥55y)
6. Tamoxifen use

Epidemiology:

With the increase in life expectancy and obesity worldwide, the incidence of endometrial cancer is also increasing [3,4]. According to 2016 statistics in our country, it is the 4th most common cancer type in women with an incidence rate of 10.5/100.000. [5] Again, according to the same data, consistent with the rest of the world, patients mostly (73.9%) are diagnosed in the early stage (I/II),
regional (Stage III) metastases are detected in 18.1% of patients and distant metastases (Stage IV) are detected in 8% of patients [5].

In endometrial cancer, the 5-year overall survival is 80% and the prognosis is generally good. However, in the presence of pelvic lymph node metastasis (LNM) at the time of diagnosis (most frequent extrauterine spread) the overall survival drops to 50% [6,7]. After treatment, the risk of recurrence is approximately 15% in cases with early-stage (I-II) endometrial cancer[8]. Approximately half of the relapse cases are local (vagina/pelvis), whereas 30% are systemic relapses and the rest are both local and systemic relapses. Most disease recurrences (68-100%) occur within the first 3 years after the end of treatment [9]. In isolated local recurrence, curative RT is the primary option if the patient has not received RT before, and surgery if the patient has received RT before [10,11]. In the presence of limited systemic recurrence, surgery is considered if it is performed without leaving a tumor behind, while chemotherapy and/or hormonal treatment is recommended in patients with the extensive systemic disease[12,13].

Findings of Endometrial Cancer

1. Abnormal bleeding, spotting: Especially the bleeding during menopause should be approached carefully. 9 out of 10 women with endometrial cancer have some type of abnormal bleeding.
2. Weight loss,
3. Pelvic pain
4. Mass.

Staging in Endometrial Cancer

Today, staging of endometrial cancer is done surgically and the FIGO (International Federation of Gynecology and Obstetrics) system, which was updated in 2009, is used [14]. As part of staging, total hysterectomy, bilateral salpingo-oophorectomy, and lymph node dissection in selected patient groups are performed. In gynecological oncology, and especially in endometrial cancer, the sentinel lymph node (SLN) concept is gaining increasing popularity and functionality. In this procedure, a dye is injected into the cervix just before the operation, and the lymph nodes holding the dye are removed in surgery, which is usually done with minimal invasive methods (robotic or laparoscopic). Thus, metastatic lymph nodes can be detected with ≤5% false-negative rates, without systemic lymph node dissection. The two handicaps of SLN are the requirement of the surgeon's experience for the success of the procedure and the immaturity of the literature on long-term survival [15].

Although endometrial cancer is seen more frequently in the postmenopausal period, 4% of patients are diagnosed under the age of 40. Hormonal therapy without hysterectomy can be given to patients in this age group who want to preserve their fertility and who meet the requirements (low-grade histology-preferably Grade 1 and no myometrial invasion detected in imaging). However, after the patient has completed their fertility or if she is unresponsive to hormonal therapy, conventional therapy should be applied [16].

According to FIGO staging, in Stage 1 disease, the tumor is confined to the uterine corpus. In stage II, the tumor has moved to the stromal layer of the cervix, but has not spread outside the uterus (in new staging, cervical glandular involvement is not taken into account). In stage III, there is spread to regional tissues (uterine serosa, adnexa, vagina, parametrium) or to regional lymph nodes (pelvic and/or paraaortic). In stage IV disease, there is distant metastasis and/or bladder/rectal mucosal involvement [14]. Although cytology included in the old staging is not included in the new staging, it has prognostic significance (Table 6).

The histological classification of endometrial cancer is made according to the World Health Organization (WHO) system [17]. The most common (77%) subtype is endometrioid carcinoma. Mixed type, serous, clear cell and mucinous carcinoma, ordered with respect to their frequency.[16] While carcinosarcomas used to be in the sarcoma group, in the new classification it has been shown that the epithelial component (carcinoma) undergoes mesenchymal transformation and forms sarcoma areas, and it is now classified as carcinoma (Table 7).

Endometrial cancer is divided into 2 subclasses according to clinical, pathological

and molecular features [18]. Type 1 cancers account for the majority of endometrial cancers and include FIGO grade 1-2 endometrioid carcinomas; they are low-grade tumors. These tumors are oestrogen sensitive, obesity is more frequently seen in patients, and a precursor lesion (atypical endometrial hyperplasia) is present in the pathogenesis. Molecularly, microsatellite instability, ras and PTEN mutations are more common. In type 1 tumors, the diagnosis is often made at an early stage and the prognosis is good. Type 2 tumors, on the other hand, include FIGO grade 3 endometrioid carcinoma and non-endometrioid histologies; they are high-grade tumors. Molecularly, p53 mutation is more common. These tumors are not oestrogen sensitive, are not associated with obesity, and usually develop on the basis of the atrophic endometrium. In type 2 tumors, extrauterine disease is more common at the time of diagnosis and the prognosis is poor. Preoperative management, surgical approach and adjuvant treatment of type 1 and 2 endometrial cancers are different from each other.

Diagnostic Methods in Endometrial Cancer

In endometrial cancer, 90% of patients present with abnormal vaginal bleeding, especially more frequently in the menopausal period [19]. Diagnosis is usually based on endometrial biopsy, which can be obtained even in outpatient settings [20]. Fractionated curettage under anesthesia is recommended in patients with ongoing complaints and normal endometrial biopsy. Hysteroscopy, on the other hand, is helpful in patients who have bleeding and who have a focal lesion (polyp, fibroid) detected on ultrasonography (USG). The first radiological imaging to be performed in a patient with abnormal uterine bleeding is pelvic USG. In this way, focal lesions that cause bleeding can be detected, and in patients with an endometrial thickness of <5mm, follow-up can be chosen as an alternative to immediate endometrial biopsy [21]. However, if the bleeding recurs, a biopsy is necessary. Although the diagnosis of endometrial cancer is usually made with endometrial biopsy material, sometimes cancer is found incidentally in hysterectomy specimens done for benign reasons. Since mesenchymal tumors (sarcoma) originate from the uterine wall, they are generally not diagnosed with endometrial sampling; similarly they are diagnosed with hysterectomy material.

According to the recommendations of the National Comprehensive Cancer Network (NCCN) 2019 guideline, lung imaging with direct radiography (X-ray) is performed after the diagnosis of endometrial cancer [15]. Pelvic magnetic resonance imaging (MRI) may be requested if the primary of tumor (cervix or uterine cancer) cannot be determined or it is

desired to evaluate the local spread of the disease. In high-grade tumors, thoracic/abdominal/pelvic computed tomography (CT) is recommended to evaluate metastatic disease. In patients with incidentally detected endometrial cancer, if any of the pathological risk factors (high-grade histological type, myometrial invasion ≥50%, cervical stromal invasion, lymphovascular invasion, tumor diameter >2cm) is present in the hysterectomy specimen, metastasis screening with thorax/abdomen/pelvic CT should be performed. If fertility-sparing therapy is to be administered, pelvic MRI is recommended to exclude myometrial invasion; USG can also be used as an alternative. Abdominal/pelvis CT or MRI scans with contrast are recommended, whereas contrast is not required in thorax imaging [15].

In patients with type 2 endometrial cancer diagnosis, serum CA125 analysis may be requested, while other tumor markers are not significant. Although an association between increased CA125 levels and LNM has been demonstrated, it is not a valuable test for predicting recurrence, but is significant in patients with baseline elevated values in the follow-up of clinical response [22,23].

Prevention and Protection

Birth control drugs have a risk-reducing effect. This protection continues for 10 years after the use of drugs. Getting diabetes under control and achieving appropriate body weight reduce the risk of endometrial cancer. If you have menopausal symptoms and considering estrogen replacement therapy, ask your doctor about the risk of endometrial cancer.

Many endometrial cancers develop over the years and as a continuation of problems, many of which are more harmless. Hyperplasia is a less serious condition due to increased growth of the endometrium. Simple hyperplasia, which is the most common, can be treated with drugs and can cause endometrial cancer with a very few rate. However, in other types of hyperplasia, the risk of developing cancer is high.

Unfortunately, there is no screening test and screening program that can be used for the early diagnosis of endometrial cancer.

How Is Endometrial Cancer Treated?

Treatment should definitely be planned and carried out by gynecologists who deal with cancer (gynecologist oncologists). After the diagnosis of endometrial cancer, there are 4 main treatment options. Surgery, radiotherapy, hormonal therapy and chemotherapy.

Surgical treatment is the main and first treatment method in many endometrial cancers.

However, sometimes a combination of these treatment methods can be used. The choice of treatment depends on the stage of the cancer.

1) Surgical treatment: There are different surgical treatment methods in the treatment of endometrial cancer. The basic surgical approach involves removal of the cervix, uterus, ovaries, and tubes, which is called abdominal hysterectomy and bilateral salpingoophorectomy.

In stages other than stage 1A and 1B of endometrial cancer, lymph node sampling (removal of some of the lymph nodes around the great vessels) is done and the lymph nodes are searched for cancer cells.

Side effects: All these surgical methods prevent the patient from having children again. Other side effects of surgical treatment are bleeding, wound infection, injury in urinary tract and bowel.

2) Radiotherapy*:* Radiotherapy is the destruction of cancerous cells by means of high-energy rays. It can be applied outside the body (external radiotherapy), or it can be applied from the vagina (barachytherapy).

The main complications of external radiotherapy are skin discoloration, diarrhea, urinary tract problems, narrowing of the vagina and pain during sexual intercourse, early menopause and weakening of the pelvic bones.

The reason for the use of radiotherapy is that it has spread outside the body of the uterus. In addition, the fact that the tumor has approached or involved the outer membrane of the uterus and it has developed from a cell type with a high risk of recurrence can be counted as another reason for radiotherapy application.

3) Chemotherapy*:* Chemotherapy in endometrial cancer is a treatment option in advanced stages (especially stage III and stage IV). It can be used together with radiotherapy after surgery. Chemotherapy is the use of drugs to destruct cancer cells. Although this varies according to the type of drug used, it has side effects such as nausea, vomiting, hair loss, susceptibility to infections, and easy fatigue. Many of the side effects disappear after

treatment.

4) Hormonal therapy: Progesterone-like drugs are used in hormonal therapy. In the treatment of these patients, ovarian removal treatment or ovarian suppression treatment after radiotherapy reduces the amount of oestrogen and reduces the growth of cancer cells.

Fertility-Preserving Treatment

If the endometrial cancer patient is in the fertile period and wants to have a child, fertility-preserving treatment may be a treatment option. However, this treatment option should be applied under certain conditions and its risks should be known precisely. It is the patient herself who will decide on this treatment, after understanding all the risks. If this treatment is chosen, the treatment should be started as soon as possible. The treatment here is complete curettage, which is the removal of the entire part of the uterine lining that needs to be removed, and high-dose hormonal therapy. Since these patients require follow-up after treatment, they should be closely monitored. After the treatment, the pregnancy process should be started as early as possible and the treatment of endometrial cancer after pregnancy should be done accurately; the aforementioned uterine removal and additional surgery must be completed.

Treatment to be Applied in Recurrence of the Disease

As with any cancer, endometrial cancer has also the risk of recurrence. The risk of recurrence varies according to the stage of the disease, the cell type from which it has originated and the grade of the cells. Where the disease recurs and what the initial treatment was will determine the course of treatment at relapse. Accordingly, surgery, chemotherapy and radiotherapy can be used alone or in combination. However, if surgery is to be performed, chemotherapy or radiotherapy should be applied following this.

Post-Treatment Follow-up

Post-treatment follow-up is very important. In the first 3 years, follow-up is done every 3-6 months. 75% of reoccurring diseases are diagnosed in the first 3 years of follow-up.

Follow-up visits include pelvic examination and examination for enlarged lymph nodes, as well as the questioning of complaints by the doctor. A Pap smear test can be useful to look for possible cancer cells in the upper part of the vagina.

If the examination shows that cancer has recurred, tests such as computed tomography, ultrasonography, CA125, blood count, or biopsy should be considered. Studies have shown that routine blood count and imaging tests are not required in the follow-up of patients without any complaints.

RESOURCES

1. Siegel RL, Miller KD, Jemal A. Cancer Statistics, 2018. CA Cancer J Clin 2018; 68:7-30.
2. D'Angelo E, Prat J. Uterin sarcoma: a review. Gynecol Oncol 2010; 116:131-139.
3. Kitchener HC, Trimble EL. Endometrial cancer state of the science meeting. Int J Gynecol Cancer 2009; 19:134-140.
4. Dinkelspiel HE, Wright JD, Lewin SN, Herzog TJ. Contemporary clinical management of endometrial cancer. Obstet Gynecol Int 2013; 2013:583891.
5. T.R. Ministry of Health TPHI Turkey Cancer Statistics. 2019.
6. Amant F, Moerman P, Neven P, Timmerman D, Van Limbergen E, Vergote I. Endometrial cancer. Lancet. 2005; 366:491–505.
7. Lewin SN, Herzog TJ, Barrena Medel NI, Deutsch I, Burke WM, Sun X, et al. Comparative performance of the 2009 international federation of gynecology and obstetrics' staging system for uterine corpus cancer. Obstet Gynecol. 2010; 116:1141–1149.
8. Fung-Kee-Fung M, Dodge J, Elit L, Lukka H, Chambers A, Oliver T, et al. Follow-up after primary therapy for endometrial cancer: a systematic review. Gynecol Oncol. 2006 Jun; 101(3):520-9.
9. Bristow RE, Purinton SC, Santillan A, Diaz-Montes TP, Gardner GJ, Giuntoli RL 2nd. Cost-effectiveness of routine vaginal cytology for endometrial cancer surveillance. Gynecol Oncol 2006; 103:709-713.
10. Jhingran A, Burke TW, Eifel PJ. Definitive radiotherapy for patients with isolated vaginal recurrence of endometrial carcinoma after hysterectomy. Int J Radiat Oncol Biol Phys 2003; 56:1366-1372.
11. -Barakat RR, Goldman NA, Patel DA, Venkatraman ES, Curtin JP. Pelvic exenteration for recurrent endometrial cancer. Gynecol Oncol 1999; 75:99-9102.
12. Altman AD, Thompson J, Nelson G, Chu P, Nation J, Ghatage P. Use of aromatase inhibitors as first and second line medical therapy in patients with endometrial adenocarcinoma; a retrospective study. J Obstet Gynaecol Can 2012; 34:664-672.
13. Awtrey CS, Cadungog MG, Leitao MM, Alektiar KM, Aghajanian C, Hummer AJ, et al. Surgical resection of recurrent endometrial carcinoma. Gynecol Oncol, 2006. 102(3):480-8.
14. Creasman W. Revised FIGO staging for carcinoma of the endometrium. Int J Gynaecol Obstet 2009; 105:103-104.
15. National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology. Version 2.2019-December 17, 2018.

16. Gunderson CC, Fader AN, Carson KA, Bristow RE. Oncologic and reproductive outcomes with progestin therapy in women with endometrial hyperplasia and grade 1 adenocarcinoma: a systematic review. Gynecol Oncol 2012; 125:477.
17. WHO Classification of tumours of female reproductive organs. Fourth Edition, Kurman RJ, Carcangiu ML, Herrington CS, Young RH (Eds), World Health Organization, 2014. p.126, 150.
18. Sherman ME. Theories of endometrial carcinogenesis: a multidisciplinary approach. Mod Pathol. 2000 Mar; 13(3):295-308.
19. American College of Obstetricians and Gynecologists. ACOG practice bulletin, clinical management guidelines for obstetrician-gynecologists, number 65, August 2005: management of endometrial cancer. Obstet Gynecol. 2005; 106(2):413.
20. 20-Dijkhuizen FP, Mol BW, Brölmann HA, Heintz AP. The accuracy of endometrial sampling in the diagnosis of patients with endometrial carcinoma and hyperplasia: a meta-analysis. Cancer. 2000;89(8):1765.
21. American College of Obstetricians and Gynecologists. The role of transvaginal ultrasonography in the evaluation of postmenopausal bleeding. ACOG Committee Opinion No.440. Obstet Gynecol. 2009; 114:409.
22. Duk JM, Aalders JG, Fleuren GJ, de Bruijn HW. CA 125: a useful marker in endometrial carcinoma. Am J Obstet Gynecol. 1986 Nov; 155(5):1097-102.
23. Patsner B, Orr JW Jr, Mann WJ Jr. Use of serum CA 125 measurement in posttreatment surveillance of early-stage endometrial carcinoma. Am J Obstet Gynecol. 1990 Feb; 162(2):427-9.

Table 6: Staging according to FIGO (International Federation Of Gynecology And Obstetrics) System in Endometrial Carcinoma

Stage I: The tumor is limited to the uterine corpus	
IA	Tumor confined to endometrium or invasion <50% is present in the myometrium
IB	The tumor invaded myometrium ≥50%
Stage II: The tumor is confined to the uterus, but has invaded the cervical stromal tissue	
Stage III: Tumor has involved uterine serosa, adnexa, vagina, parametrium or regional lymph nodes **nodes**	
IIIA	Uterine serosa and/or adnexal involvement
IIIB	Vaginal and/or parametrial involvement
IIIC	Regional (pelvic and/or paraaortic) lymph node involvement
IIIC1	Pelvic lymph node involvement
IIIC2	Paraaortic lymph node involvement (with or without pelvic lymph node involvement)
Stage IV: Distant metastasis or bladder/rectal involvement	
IVA	Tumor has invaded bladder/rectal mucosa
IVB	Distant metastasis (including inguinal lymph nodes, intraperitoneal disease, lung, liver or bone metastasis)

Table 7: Histopathologic Types of Uterine Cancer according to the classification of the World Health Organisation

Epithelial tumors (Carcinoma)	Endometrioid, mucinous, serous, clear cell, neuroendocrine tumors (low/high- level), mixes, undifferentiated, dedifferentiated
Mesenchymal tumors (Sarcoma)	Leiomyosarcoma, Endometrial stromal sarcoma (low/high-level), Rhabdomyosarcoma
Mixed epithelial – mesenchymal tumors	Adenosarcoma, carcinosarcoma
Lymphoid and myeloid tumors	Lymphomas, myeloid neoplasms
Secondary tumors	

2.9. Kidney Cancer

Kidney Cancer (Renal Cell Carcinoma)

Epidemiology

Kidney cancer is the third most common tumor of the genitourinary system after prostate and bladder cancer. Renal cell carcinoma is the most common solid tumor of renal origin, originating from the renal cortex and is responsible for 80-85% of all kidney cancers. The most common type of renal cell cancer is clear cell adenocarcinoma. Less frequently, papillary vechromophobe tumors occur. Transitional cell carcinoma originating from the renal pelvis is seen in approximately 8% of cases. International cancer research agency statistics (GLOBOCAN) has published the latest 2018 data. Kidney cancer ranks 16th in the world with an estimated 403,000 new cases and 175,000 deaths, according to Globocan 2018 data. Kidney cancer is more common in men compared to women. Incidence and mortality rates, respectively; 6.0 and 2.6 per 100,000 for men; 3.1 and 1.1 per 100,000 in women [1]. Although the incidence of kidney cancer varies between regions around the world, it is most frequently seen in the Czech Republic and North America [2]. In the United States, it is more common among Native Americans, Alaska Natives, Hispanic Latinos and Whites [3]. In our country, according to the 2016 data of Cancer Statistics of Turkey, when the age-standardized rate distribution of cancers by sex (Turkey Combined Database, 2016) (World Standard Population, per 100,000 people) is analyzed, kidney cancer is seen at a rate of 7.4 per 100,000 in men, while it is seen at a rate of 3.7 per 100,000 in women. While kidney cancer is the 6th most common cancer in men, it is not among the top 10 most common cancers in women [4]. Renal cell carcinoma is most common between the 6th and 8th decades. According to the 2003-2007 National Cancer Institute (NCI) Surveillance, Epidemiology and End Results (SEER) cancer data, the median age at diagnosis is 64 years [5]. According to the data obtained from SEER records covering the years 2009-2015, the disease is seen as 65% localized, 17% regional, 16% metastatic, and 3% unstaged[6]. The incidence of renal cell cancer has increased more than 3 times compared to mortality. This is because tumors can be detected in smaller sizes (<4 cm) at an early stage and there are curative treatment options [6,7].

Risk Factors

Smoking is a risk factor that increases kidney cancer. The risk is greatest in active smokers, and the incidence of advanced disease is high in this group [8]. It creates an increased risk in the development of kidney cancer independent of the use of antihypertensive in hypertension and obesity [9]. Increased body weight increases the risk of kidney tumors in both men and women[10]. The risk of acquired cystic disease increases in patients undergoing long-term dialysis. Chronic kidney disease and acquired cystic disease also increase the risk of renal cell cancer by approximately 30 times [11]. Polycystic kidney disease is a renal disease that increases the tendency to cancer. Occupational exposure to cadmium, asbestos, and petroleum products also increases the risk [12]. Von Hippel Lindau disease is an autosomal dominant disease with mutations in the 3p chromosome. Deletion in this chromosome is associated with the risk of clear cell cancer. It causes especially sporadic cases of cancer [13]. Long-term use of phenacetin and aspirin causes chronic renal failure and increases the risk of the renal pelvis and urothelial cancer[14]. Those who received cytotoxic chemotherapy for cancer treatment in childhood, those with autoimmune diseases, and those who underwent bone marrow transplantation are at risk of developing kidney cancer[15]. An epidemiological study has shown that chronic hepatitis C infection increases the risk of kidney cancer [16]. Patients with sickle cell anemia also have an increased risk of kidney medullary cancer. It has been shown that a history of kidney stones is associated with an increased risk for both renal cell cancer and transitional cell cancer originating from the upper urinary tract [17].

Clinical Findings, Diagnosis and

Staging Clinical Findings

At the time of diagnosis, approximately 25% of patients are in the locally advanced or metastatic stage. Patients are asymptomatic until advanced disease. The most common symptoms are hematuria, abdominal mass, and pain. This triad occurs in 9% of patients and usually indicates locally advanced disease [18]. Unilateral, sudden onset varicocele indicates invasion of the inferior vena cava and renal vena and is a rare case [19]. The most common regions of involvement in metastatic disease include the lungs, lymph nodes, bone, liver, and brain. In the diagnosis, the renal mass is evaluated by tomography and a diagnostic biopsy is done from the most suitable and easily accessible area.

Clinically, patients with kidney cancer may apply paraneoplastic symptoms due to ectopic hormone production. Anemia of chronic disease may be seen. Fever, weight loss, and fatigue are seen due to impaired liver function tests, which indicates a poor prognosis [20]. Nephrectomy can improve hepatic dysfunction. Calcium elevation can be observed in laboratory values in 15% of patients with kidney cancer. This may be due to lytic bone metastases and secretion of Parathyroid hormone-related protein (PTHrp) [21]. Due to the production of erythropoietin, erythrocytosis can be seen at a rate of 1-5%. It may also rarely present with hypertension, amylysis, thrombocytosis, or polymyalgia rheumatica.

Diagnosis

Staging

Tomography is very important in showing the spread to neighboring organs. Among other imaging methods, bone scintigraphy is indicated in cases of bone pain and elevated serum alkaline phosphatase. Bone metastases in kidney cancer have mostly lytic characteristic. Bone scintigraphy may give false-negative results because lytic metastases are more common than blastic ones. Lung tomography is useful to evaluate lung metastases and mediastinal lymph nodes. MR imaging is more appropriate to evaluate vena cava inferior or right atrium involvement [22]. Positron emission tomography (PET-CT) imaging is also highly specific in demonstrating the primary lesion.

The eighth edition (2017) of the tumor, node, metastasis (TNM) system is used in staging. The TNM system is supported by the American Joint Committee on Cancer (AJCC) and the International Association for Cancer Control (UICC) [23]. The most important factor determining the prognosis is the stage of the disease.

In this system, tumors confined to the kidney are classified as T1 or T2, according to their size (T1 <7 cm; T2>7 cm). T3 tumor extends to renal vein or perinephrtic tissues (adrenal gland and perinephric adipose tissue). T4 tumor exceeds Gerota fascia. The stage changes according to the presence of nodal involvement or metastasis.

Apart from TNM staging, the patient's performance score and the widely used Fuhrman grading system, which evaluates the nuclear size, contour, and nucleolar structure, also play an important role in prognosis [24].

The Metastatic Kidney Cancer Database Consortium (IMDC) risk model is a 6-factor risk model used in stage 4 diseases that are treated with anti-vascular endothelial growth factor (Anti-VEGF). In this scoring system, risk factors are: Karnofsky performance score being <80, time from diagnosis to treatment is <12 months, hemoglobin value lower than the lower limit of normal, serum calcium value higher than the upper limit of normal, absolute neutrophil count above the upper limit of normal and the platelet count above the upper limit of normal. It is defined as a favorable or low-risk disease if no risk factors are present, intermediate-risk disease if one or two risk factors are present, and poor or high-risk disease if three to six risk factors are present. This risk score shows resistance to anti-VEGF therapy and guides for second-line therapy. Prognostic risk scoring is important also in the selection of immunotherapy treatment [25].

Treatment

Those who are candidates for surgery in kidney cancer are patients who can be cured. While radical nephrectomy is performed in tumors larger than 7 cm, partial nephrectomy is preferred in tumors smaller than 7 cm and in the presence of chronic kidney disease with the risk of undergoing postoperative dialysis. Retroperitoneal lymph node dissection should also be performed in patients who have undergone radical nephrectomy. In the case of inferior vena cava involvement, surgery is preferred so that thrombectomy can also be performed.

In patients who are not suitable for surgery, embolization of the primary tumor can be performed to control symptoms [26]. Embolization is an advantageous treatment, especially in elderly patients and patients with high comorbidities. In metastatic disease, if the area of metastasis is suitable for local treatment, it can be treated with methods such as local surgery, radiotherapy or embolization.

Adjuvant therapy is not recommended in completely resected kidney cancer. Only in high-risk patients, sunitinib, a targeted therapy agent that has been shown to benefit disease-free survival, can be considered [27].

Immunotherapy and/or molecular targeted therapies are used in the treatment of metastatic clear cell kidney cancer. In targeted therapy, vascular endothelial growth factor and mammalian target of rapamycin (mTOR pathway) are the most important targets in kidney tumors with high blood supply. Antiangiogenic agents are sunitinib, sorafenib, pazopanib, cabozantinib, lenvatinib, and the monoclonal antibody bevacizumab [28]. Immunotherapies, which have been used in recent years, constitute the agenda in oncological treatment, with their good treatment results, especially in immunogenic tumors such as kidney cancer. The main mechanism in this treatment is to ensure that the immune system is active against the tumor cell, by inhibiting the checkpoints that prevent the excessive and uncontrolled response of the immune system. Active surveillance is an option in asymptomatic disease, which is in the naive good-risk group. In this patient group with a limited disease burden, anti-angiogenic targeted therapy with single-agent vascular endothelial growth factor (VEGF) inhibitors is also a treatment option. However, if the patient is symptomatic and the disease is a rapidly progressive one, the preferred options for combination immunotherapy regimens for treatment include the combination of nivolumab and ipilimumab or the combination of pembrolizumab and axitinib. In patients in moderate and bad risk groups, combined treatments with immunotherapy are recommended in the initial period.

RESOURCES

1. Bray F, Ferlay J, Soerjomataram I, et al. Global CancerStatistics 2018: GLOBOCAN Estimates of IncidenceandMortalityWorldwidefor 36 Cancers in 185 CountriesCaCancer J Clın 2018; 68:394–424.
2. Chow WH, Dong LM, Devesa SS. Epidemiologyand risk factorsforkidneycancer. NatRevUrol 2010; 7:245.
3. Siegel R, Naishadham D, Jemal A. Cancerstatistics, 2012. CA Cancer J Clin 2012; 62:10.
4. Ministry of Health Ankara Local Health Authority, Turkey Cancer Statistics 2016, Ankara 2019.
5. Thompson RH, Ordonez MA, Iasonos A, et al. Renalcellcarcinoma in youngandold patients- is there a difference? J Urol 2008; 180:1262.
6. Hollingsworth JM, Miller DC, Daignault S et al. Risingincidence of smallrenalmasses: a needtoreassesstreatmenteffect. J NatlCancerInst 2006; 98:1331.
7. Ries LA, Eisner MP, Kosary CL, et al. SEER CancerStatisticsReview, 1973-1997, NationalCancerInstitute, Bethesda 2000.

8. Cumberbatch MG, Rota M, CattoJW,et al.The Role of TobaccoSmoke in BladderandKidneyCarcinogenesis: A Comparison of Exposuresand Meta-analysis of IncidenceandMortalityRisks. EurUrol 2016; 70:458.
9. Hidayat K, Du X, Zou SY, Shi BM. Blood pressureandkidneycancer risk: meta-analysis of prospectivestudies. J Hypertens 2017; 35:1333.
10. Pischon T, Lahmann PH, Boeing H, et al. Body size and risk of renalcellcarcinoma in the EuropeanProspectiveInvestigationintoCancerandNutrition (EPIC). Int J Cancer 2006;118:728.
11. Brennan JF, Stilmant MM, Babayan R K,et al. Acquiredrenalcysticdisease: İmplicationsfortheurologist. Br J Urol 1991; 67:342.
12. Mandel JS, McLaughlin JK, Schlehofer B, et al. International renal-cellcancerstudy. IV.Occupation. Int J Cancer 1995; 61:601.
13. Yao M, Yoshida M, Kishida T, et al. VHL tumorsuppressor gene alterationsassociatedwithgoodprognosis in sporadicclear-cellrenalcarcinoma. J NatlCancerInst 2002; 94:1569.
14. Sørensen HT, Nørgård B, Friis S, et al. [Non-steroidal anti-inflammatoryagentsand prevention of colorectalcancerandothertypes of cancer]. UgeskrLaeger 2003; 165:1260.
15. Argani P, Laé M, Ballard ET, et al. Translocationcarcinomas of thekidneyafter chemotherapy in childhood. J ClinOncol 2006; 24:1529.
16. Gordon SC, Moonka D, Brown KA, et al. Risk forrenalcellcarcinoma in chronichepatitis C infection. CancerEpidemiolBiomarkersPrev 2010; 19:1066.
17. Cheungpasitporn W, Thongprayoon C, O'Corragain OA, et al. The risk of kidneycancer in patientswithkidneystones: a systematicreviewand meta-analysis. QJM 2015; 108:205.
18. Skinner DG, Colvin RB, Vermillion CD, et al. Diagnosisandmanagement of renalcell carcinoma. A clinicalandpathologicstudy of 309 cases. Cancer 1971; 28:1165.
19. Pınals RS, Krane SM. Medicalaspects of renalcarcinoma. PostgradMed J 1962;38:507.
20. Boxer RJ, Waisman J, Lieber MM, et al. Non-metastatichepaticdysfunctionassociatedwithrenalcarcinoma. J Urol 1978; 119:468.
21. Lytton B, Rosof B, Evans JS. Parathyroidhormone-likeactivity in a renalcarcinomaproducinghypercalcemia. J Urol 1965; 93:127.
22. Semelka RC, Shoenut JP, Magro CM, et al. Renalcancerstaging: comparison of contrastenhancedCT andgadolinium-enhancedfat-suppressedspin-echoandgradient-echo MR imaging. J MagnResonImaging 1993; 3:597.
23. Rini BI, McKiernan JM, Chang SS, et al. Kidney. In: AJCC CancerStaging Manual, 8th, AminMB (Ed), Springer, New York 2017. p.739.

24. Fuhrman SA, Lasky LC, Limas C. Prognosticsignificance of morphologicparameters in Renalcellcarcinoma. Am J SurgPathol 1982; 6:655.
25. Ko JJ, Xie W, Kroeger N, et al. The International MetastaticRenal Cell Carcinoma Database Consortium model as a prognostictool in patientswithmetastaticrenalcellcarcinomapreviouslytreatedwithfirst-linetargetedtherapy: a population-basedstudy. LancetOncol2015; 16:293.
26. Maxwell NJ, Saleem Amer N, Rogers E, et al. Renalarteryembolisation in thepalliativetreatment of renalcarcinoma. The British journal of radiology. 2007; 80:96-102.
27. Motzer RJ, Ravaud A, Patard JJ, et al. AdjuvantSunitinibfor High-risk Renal Cell CarcinomaAfterNephrectomy: SubgroupAnalysesandUpdatedOverallSurvivalResults. EurUrol 2018; 73:62-68.
28. Atkins MB. Management of advancedrenalcancer. KidneyInt 2005; 67:2069.

2.10. Non-Hodgkin Lymphoma

Definition

Lymphomas include a range of malignant lymph node diseases that develop from cells naturally found in lymphoid tissues, with a wide clinical course ranging from a slow clinical course to a very aggressive one [1].

Epidemiology

About 15% of all lymphomas are Hodgkin lymphoma and 85% are non-Hodgkin lymphoma (Non-Hodgkin lymphoma= NHL) [1]. Its incidence is 17 per 100,000 [2]. According to Turkish cancer statistics, 10,847 NHL cases were seen in Turkey in 2015 [3]. It can be seen in people of all ages and races. Although Burkitt lymphoma and lymphoblastic lymphoma usually occur in younger patients, the average age at diagnosis in NHL patients is 60 years or older [1].

Disease Etiology

Non-Hodgkin lymphomas can originate from B-cell precursors, T-cell precursors, mature B-cells, mature T-cells, or rarely natural killer (NK) cells. Most commonly, cases of NHL originating from B lymphocytes are seen (85% of B-cell origin, 15% of T or NK-cell origin). There are findings that various infections, immune deficiency and/or autoimmune disease conditions, chronic inflammation, familial background, environmental factors, and

chromosomal abnormalities are effective in the development of lymphoma [2,4-6].

1. **Environmental factors:** The frequency of lymphoma has been reported more frequently in rubber industry workers and those exposed to arsenic and asbestos. Similarly, it has been reported that the frequency of lymphoma is increased in people exposed to radiation and in patients receiving radiotherapy and chemotherapy.

2. **Immune disorders:** Syndromes with congenital and acquired immunodeficiency are risk factors for lymphoma. An increased incidence of NHL has been found in patients receiving immunosuppressive (immunosuppressive) therapy.

3. **Autoimmune diseases:** Autoimmune diseases such as rheumatoid arthritis, Celiac disease, Sjögren's syndrome, Hashimoto's thyroiditis have been reported to be risk factors for lymphoma.

4.Infectious agents: Various infectious agents have been associated with some NHL subtypes: Ebstein Barr Virus (EBV) (Burkitt lymphoma), Human T-Cell Virus (HTLV-1) (Adult T-cell leukemia-lymphoma), Human Herpes Virus (HHV)-8 (primary effusion lymphoma, post-transplant lymphoproliferative disease), Hepatitis C Virus (HCV) (splenic marginal zone lymphoma), Human Immunodeficiency Virus (HIV) (Diffuse Large B-Cell Lymphoma, Burkitt lymphoma), Helicobacter Pylori (gastric MALT lymphoma), Borrelia Burgdorferi (cutaneous MALT lymphoma)

5. Drugs, chemicals: In various studies, phenytoin, methotrexate, chemotherapeutic drugs, and hair dye have been accused as risk factors for lymphoma.

6. **Cytogenetic and molecular disorders:** Some genetic changes that can be seen in NHL subtypes include:

t (14,18) (Follicular lymphoma)

t (8,14), t(2,8), t(8,22) (Burkitt

lymphoma) t (11,14) (Mantle cell

lymphoma)

t (2,5) (Anaplastic large cell lymphoma) t

(11,18) (MALT lymphoma)

Classification

Today, the most commonly used classification is a system organized by the World

Health Organization (WHO), which categorizes by considering age and place of involvement, as well as histology, immunophenotype and genotype [2]. WHO classification of mature lymphoid neoplasms 2016 is summarized in Table 8 and the WHO classification of lymphoblastic leukemia/lymphoma is summarized in Table 9.

Table 8. WHO Classification of Mature Lymphoid Neoplasms 2016 [7]

Mature B-Cell Lymphomas
B-cell chronic lymphocytic leukemia/ small lymphocytic lymphoma
Monoclonal B-cell lymphocytosis
B-cell prolymphocytic leukemia
Lymphoplasmocytic lymphoma
Splenic marginal zone B-cell lymphoma
Hairy Cell Leukemia
Monoclonal gammopathy of undetermined significance
Plasma cell myeloma
Bone plasmacytoma
Extra-bone plasmacytoma
Extranodal marginal zone B-cell lymphoma of mucosa-related lymphoid tissue (MALT lymphoma)
Nodal marginal zone B-cell lymphoma
Follicular lymphoma
Primary cutaneous follicle centre lymphoma
Mantle cell lymphoma
Diffuse large B-cell lymphoma
T-cell histiocyte-rich large B-cell lymphoma
Diffuse large B-cell lymphoma of the central nervous system
Primary cutaneous Diffuse large B-cell lymphoma, leg type
Diffuse large B-cell lymphoma associated with chronic inflammation
Lymphomatoid granulomatosis

Mediastinal large B-cell lymphoma
Intravascular large B-cell lymphoma
ALK-positive large B-cell lymphoma
Plasmablastic lymphoma
Primary effusion lymphoma
Burkitt lymphoma / Burkitt cell leukemia
B-cell lymphoma, unclassifiable, with features between diffuse large B-cell lymphoma and classic Hodgkin lymphoma
Mature T- and NK-Cell Neoplasms
T-cell prolymphocytic leukemia
T-cell large granular lymphocytic leukemia
Aggressive NK-cell leukemia
Adult T-cell lymphoma/leukemia
Extranodal NK/T-cell lymphoma, nasal type
Enteropathy-associated T-cell lymphoma
Hepatosplenic T-cell lymphoma
Subcutaneous panniculitis-like T-cell lymphoma
Mucosis Fungoides
Caesarean Syndrome
Primary cutaneous CD30+ T-cell lymphoproliferative disorders
Anaplastic large cell lymphoma, ALK positive
Anaplastic large cell lymphoma, ALK negative
Peripheral T-cell lymphoma, not otherwise specified
Angioimmunoblastic T-cell lymphoma

ALK, anaplastic lymphoma kinase

Table 9. WHO Classification of Lymphoblastic Leukemia/Lymphoma 2016[8]

B-lymphoblastic leukemia/ lymphoma
B-lymphoblastic leukemia/ lymphoma, not otherwise specified
B-lymphoblastic leukemia/lymphoma with recurrent genetic abnormalities t (9;22)(q34.1;q11.2); BCR-ABL1-like B-lymphoblastic leukemia/lymphoma t(v;11q23.3); B Lymphoblastic Leukemia/Lymphoma with KMT2A rearranged t(12;21)(p13.2;q22.1); B-lymphoblastic leukemia/ lymphoma with ETV6-RUNX1 B-lymphoblastic leukemia/ lymphoma with hyperdiploidy B-lymphoblastic leukemia/lymphoma with hypodiploidy B-lymphoblastic leukemia/ lymphoma with t(5;14)(q31.1;q32.3) t(1;19)(q23;p13.3); B-lymphoblastic leukemia/ lymphoma with TCF3-PBX1
Provisional entity: BCR-ABL1-like B-lymphoblastic leukemia/ lymphoma
Provisional entity: B-lymphoblastic leukemia/ lymphoma with iAMP21
T-lymphoblastic leukemia/ lymphoma
Provisional entity: Early T-cell precursor lymphoblastic leukemia/ lymphoma
Provisional entity: NK cell lymphoblastic leukemia/ lymphoma

The clinical courses of lymphoid malignancies were not considered in the WHO classification. However, some clinical studies have classified lymphoid malignancies according to their clinical behavior. According to the clinical course, NHL can be divided into 3 groups as indolent (slow course), aggressive, and very aggressive.

- Indolent lymphomas: Even when these patients are untreated, their survival is often measured in years. They constitute 35-40% of NHLs [9].
- Aggressive lymphomas: If these patients are left untreated, their survival is usually measured in months. They make up about half of NHLs [9].
- Very Aggressive: If these patients are left untreated, their survival periods are usually limited to weeks. 5% of NHLs are very aggressive.

Indolent, aggressive, and very aggressive lymphomas are summarized in Table -10 [10].

Table 10. Classification of NHL According to Traits of Clinical Course

Indolent Lymphomas
B-cell neoplasms
Small lymphocytic lymphoma / B-cell chronic lymphocytic leukemia
Lymphoplasmocytic lymphoma (± Waldenstrom's macroglobulinemia)
Hairy cell leukemia
Follicular lymphoma (grade I and II)
Marginal zone B-cell lymphoma
Mantle cell lymphoma
Plasma cell myeloma/plasmacytoma
T-cell lymphomas
T-cell large granular lymphocytic leukemia
Mycosis Fungoides
T-cell prolymphocytic leukemia
NK-cell neoplasms
NK-cell large granular lymphocytic leukemia
Aggressive Lymphomas
B-cell neoplasms
Follicular lymphoma (grade 3)
Diffuse large B-cell lymphoma
Mantle cell lymphoma*
T-cell neoplasms
Peripheral T-cell lymphoma
Anaplastic large cell lymphoma

Very Aggressive Lymphomas
B-cell neoplasms
Burkitt lymphoma
Precursor B-cell leukemia/lymphoma
T-cell neoplasms
Adult T-cell leukemia/lymphoma
Precursor T lymphoblastic leukemia/lymphoma

*Mantle cell lymphoma may have an indolent course or may be associated with an aggressive clinic.

Clinic

Aggressive or very aggressive lymphomas usually present with a rapidly growing mass. Fever, night sweats and/or weight loss may be present. Indolent lymphomas are usually insidious. It presents itself with slow-growing lymphadenopathy (an abnormality in the size and character of the lymph node), hepatomegaly (enlarged liver), splenomegaly (enlarged spleen), and/or cytopenia (decreased blood count) over months or years. In most patients, superficial, asymmetrical, rubbery, mobile, painless lymph enlargement is seen in one or more peripheral lymph node regions [2]. Bone marrow, skin, gastrointestinal tract, central nervous system, and bone involvement may be present as extra-lymph node disease (extranodal). Compression symptoms due to dysfunction of the involved organ or lymphadenopathy may occur (such as bowel obstruction, obstructive uropathy, spinal cord compression). Skin involvement is frequently seen in NK/T cell-derived lymphomas. They can lead to many skin findings that differ from each other, from erythema to papular, nodular lesions, and even a vasculitis-like appearance. The disease,
which is present in the oropharyngeal lymphoid structures in 5-10% of patients, can cause sore throat, noisy breathing, and shortness of breath. Anemia-related symptoms (weakness, heart palpitations, pale appearance), infections sourcing from neutropenia, or mucosal and subcutaneous hemorrhages due to thrombocytopenia may be the initial sign, especially in patients with diffuse bone marrow involvement [2].

Diagnostic Procedures

Detailed history and physical examination are important. The extent and location of the disease should be investigated. Symptoms indicating possible involvement should be investigated in detail. Peripheral lymph nodes, spleen and liver, non-lymph node involvement areas should be examined. B symptoms such as fever, weight loss, and night sweats should be analyzed. Concomitant diseases should be evaluated. In all patients, complete blood count, liver and kidney function tests and electrolytes, LDH, uric acid should be checked, and viral serological evaluation (HBV, HCV, HIV-1/2) should be performed. To exclude bone marrow involvement, a unilateral bone marrow biopsy is recommended. Lumbar puncture and cytology should be performed in patients with suspected central nervous system involvement. For imaging purposes, PA-lung X-ray, chest, abdomen, and pelvis contrast computed tomography (CT) and/or Positron Emission Tomography (PET) are recommended. PET/CT is a valuable non-invasive imaging modality for staging, prognosis, and evaluation of response to treatment. If necessary, gastrointestinal endoscopy/colonoscopy and brain tomography can be performed. Excisional lymph node biopsy should be done to determine the diagnosis and the histological subtype of the disease. Adequate material should be provided for immunophenotyping and genetic studies. For an accurate diagnosis, the results obtained using techniques such as microscopic examination, immunohistochemistry, immunophenotyping, conventional cytogenetics, molecular genetics, and fluorescent in situ hybridization (FISH) should be evaluated together with clinical data. Not only morphological studies but also genetic and molecular studies should be performed from both bone marrow (in the presence of involvement) and lymph node biopsy. This is important in terms of prognosis as well as diagnosis. Immunophenotype determination is extremely important in the differential diagnosis of lymphomas, prognosis, and treatment determination. The characteristic immunophenotype features in the common B-cell NHL are summarized in Table 11 [2].

Table11. Characteristic Immunophenotypic Features in Common B-Cell NHL [2]

	sIg	CD20	CD5	CD10	CD23	BCL6	MUM1
SLL/KLL	weak	+	+	-	+	-	-
LPL	+	+	-	-	-	-	+
MALT lymphoma	+	+	-	-	+/-	-	+/-
FL	+	+	-	+	+/-	+	-
MCL	+	+	+	-	-	-	-
DLBCL, GCB	+/-	+	-	-		+	-
DLBCL, ABC	+/-	+	-	-		-	+
Burkitt lymphoma	+	+	-	+	-	+	-

ABC, activated B-cell type; DLBCL, Diffuse large B-cell lymphoma; FL, Follicular lymphoma; GCB, germinal center B-cell type; CLL, chronic lymphocytic leukemia; LPL, lymphoplasmacytic lymphoma; MALT, mucosa-associated lymphoid tissue; MCL, mantle cell lymphoma; MUM1, lymphocyte-specific transcription factor; SIg, surface immunoglobulin; SLL, small lymphocytic lymphoma

Staging

Before starting treatment, staging should be done. The treatment approach is determined according to the stage determined for the patient. The Lugano Classification used in NHL staging is given in Table 12 [11].

Table 12. Revise Staging System fo Primary Nodal Lymphomas (Lugano Classification)

STAGE	DISEASE AREAS
I	A single lymph node area
IE	Single extralymphatic involvement without nodal involvement
II.	Two or more lymph node regions on the same side of the diaphragm
IIE	Limited extralymphatic involvement in addition to the stage I or II
III.	Involvement in lymph node regions on both sides of the diaphragm
IV.	Diffuse involvement with or without LN involvement in one or more extralymphatic organs

Treatment approach

For diagnosis, it is required to take an adequate biopsy specimen from the site of the disease and make a pathological examination, because the clinical manifestations, course, and treatment of lymphomas vary greatly according to the type of lymphoma. A cardiac evaluation is recommended for all patients, particularly those with advanced age and comorbidities, before initiating treatment. A pregnancy test should be done on women of childbearing age. Because of the risk of infertility, reproductive counseling should be given to young patients, fertility problems and sperm bank opportunities should be discussed for patients of childbearing potential, and sperm freezing and storage should be considered if chemotherapy or pelvic radiotherapy is considered. The patient's performance status (ECOG score or Karnofsky index) should be determined. Pulmonary function test should be performed if necessary.

1. Watch-and-see

Some patients with early-stage and asymptomatic indolent lymphoma can be followed without treatment.

2. Chemotherapy

Treatment is usually a combination that a monoclonal antibody and chemotherapy drugs are used together against tumor cells [11]. The use of a combination of rituximab, cyclophosphamide, adriablastine, vincristine, and prednisolone (R-CHOP) as first-line therapy remains the standard approach in the treatment of diffuse large B-cell lymphoma, which is the most common aggressive NHL.

3. Monoclonal Antibody Therapy

85% of NHL cases are of B-cell origin, and the addition of antibodies against CD20 to the therapy for these patients improves response rates and survival. Rituximab is the first agent used and can be used intravenously or subcutaneously. Ofatumumab and obinituzumab are also anti-CD20 specific antibodies. Antibodies against CD30 are also used in anaplastic large cell lymphomas [2].

4. Radiotherapy

In lymphomas, radiotherapy (radiation therapy) can be applied to symptomatic disease areas for palliation or in stage 1-2 slow-progressing lymphomas. Cranial irradiation is an important part of treatment in primary brain lymphomas and leptomeningeal involvement.

5. Stem Cell Transplantation

In relapsed/resistant lymphomas, first salvage therapy followed by high-dose chemotherapy with autologous stem cell transplantation and, in selected cases, allogeneic stem cell transplantation should be performed. Autologous stem cell transplantation can be applied in some aggressive lymphomas in the first remission.

6. Treatment options in resistant cases

Lenalidomide (immunomodulator), ibrutinib (bruton tyrosine kinase inhibitor), bortezomib (proteasome inhibitor), venetoclax (bcl-2 inhibitor), acalubrutinib, idelalisib (phosphoinositide 3-kinase inhibitor), obinutuzumab (anti-CD20 monoclonal antibody), ofatumumab (anti-CD20 monoclonal antibody), inotuzumab ozogamicin (anti-CD20 monoclonal antibody), fostamatinib (Syk inhibitor) are drugs that can be used as an alternative to or in combination with chemotherapy regimens. Promising results have been reported with cellular therapy methods produced by genetic engineering(for example,

CAR-T cells) developed in recent years for target antigens.

Evaluating Response to Treatment

It is based on the size reduction response of enlarged lymph nodes to treatment seen on computed tomography and the evaluation of the response of bone marrow involvement to treatment. Evaluation of response to treatment is made according to the Lugano criteria [11]. Response categories are divided into total response, partial response, unresponsive or stable disease, and progressive disease.

Today, PET/CT is used in response evaluation in aggressive NHLs. It is recommended to use the 5-point Deauville criteria when evaluating the PET examination. Lugano criteria are summarized in Table 13.

Table 13. Lugona Criteria for Evaluation of Lymphoma Response [11]

Response and Region	**PET/CT-based response**	**CT-based response**
Total response	Complete metabolic response	Complete radiological response (all of the below)
Lymph Nodes and Extralymphatic Regions	A score of 1, 2, 3* on a 5-point scale, irrespective of the presence of a residual mass	Reduction of the long diameter (LDi) of the involved nodes to ≤1.5 cm Absence of extralymphatic region involvement
Immeasurable Lesions	Not applicable	NA
Organ enlargement	Not applicable	Should be back to normal
New Lesions	NA	NA
Bone Marrow	There should be no FDG uptake in the bone marrow	Should be morphologically normal
Partial	Partial metabolic response	Partial remission (all of the below)

Lymph Nodes and Extralymphatic Regions	Residual mass of any size and lesion with reduced uptake compared to baseline, with a score of 4, 5 In the interim evaluation, this means responsive disease. At the end of the treatment, it means a residual mass.	≥50% reduction in SPD size of up to 6 measurable nodal and extranodal sites
Immeasurable Lesions	Not applicable	None/normal, regression, no increase
Organ enlargement	Not applicable	Spleen size should be >50% reduced compared to normal
New Lesions	NA	NA
Bone Marrow	There is a higher rate of FDG involvement than normal bone marrow, but it is decreased compared to baseline	Not applicable
Unresponsive or stable disease	With no metabolic response	Stable disease
Lymph Nodes and Extralymphatic Regions	Based on the interim or post-treatment evaluation, the score is 4-5, with no significant change in FDG involvement	<50% reduction in SPD size of up to 6 dominant measurable nodal and extranodal regions and no criteria for progressive disease
Immeasurable Lesions	Not applicable	No increase consistent with progression
Organ enlargement	Not applicable	No increase consistent with progression
New Lesions	NA	NA

Bone Marrow	No change compared to baseline	Not applicable
Progressive disease	Progressive metabolic disease	To be a progressive disease, at least one of the following must be present.
Nodal masses	Score 4 or 5 lesions with increased FDG involvement intensity compared to baseline, or newly developed lesions	PPD progression
Extranodal lesions	New FDG involvements consistent with lymphoma at interim evaluation or at the end of treatment	To be considered involvement, the lesion must be: long diameter (LDi) >1.5 cm and ≥50% increase in PPD nadir and Increase in size of long (LDi) or short diameter (SDi) relative to nadir 0.5 cm for lesions ≤2 cm 1.0 cm for lesions >2 cm In the presence of splenomegaly, an increased length of >50% relative to baseline. If there is no previous splenomegaly, at least 2 cm increase compared to baseline. New or recurrent splenomegaly
Immeasurable Lesions	NA	Newly developed lesions or progression of pre-existing unmeasurable

		lesions
New Lesions	New FDG involvement compatible with lymphoma	Regrowth of previously regressed lesions New lymph node >1.5 cm in any axis New extranodal area >1.0 cm in any axis Evaluable disease of any dimension that is definitively attributable to lymphoma
Bone Marrow	New or relapsed bone marrow involvement	New or relapsed bone marrow involvement

FDG, fluorodeoxyglucose; LDi, longest horizontal diameter of a lesion; PET, positron emission tomography; Cross measurement of PPD, LDi, and vertical diameter; SDi is the shortest diameter perpendicular to LDi; SPD, the sum of the vertical diameters of multiple lesions

* In many patients, a score of 3 indicates a good prognosis with standard treatment, especially at the interim evaluation. However, in studies involving PET which analyzes de-escalation, it may be preferable to consider a score of 3 as an inadequate response (to avoid inadequate treatment).

Prognosis

Early identification of high- and low-risk patients in terms of response to treatment is of great importance in determining the treatment approach. For ease of application, prognostic indexes consisting of data that can be obtained with the routine investigation and examination findings have been developed.

1. Prognostic Scorings Used for Diffuse Large B-Cell Lymphoma

1. 1. International prognostic index (IPI)

1. Age >60
2. Serum LDH level above normal
3. ECOG performance status ≥ 2
4. Ann Arbor stage 3 or 4
5. Number of non-lymph node involved areas >1

In the presence of the above criteria, each receives 1 point.

The survival times received with respect to IPI scores, when 1063 patients with CD20-positive aggressive lymphoma received rituximab and CHOP or CHOP-like chemotherapy, are given in Table 14 [12].

Table 14. Survival Time According to IPI Scores for Aggressive NHL

Score	Risk group	3-year PFS	3-year OS
0-1	Low risk	87%	91%
2	Low-medium risk	75%	81%
3	High-medium risk	59%	65%
4-5	High risk	50%	59%

OS, overall survival; PFS, progression-free survival

1.2. Age-adjusted International Prognostic Index (aaIPI)

1. Serum LDH level, above normal
2. ECOG performance status ≥ 2
3. Ann Arbor stage 3 or 4

In the presence of the above criteria, each receives 1 point. Survival times according to aaIPI scores are given in Table 15 [13].

Table 15. Survival Time According to Age-adjusted IPI (aaIPI) Scores for Aggressive NHL

Score	Risk group	TR rate	5-year OS

0	Low	91%	56%
1	Low-medium	71%	44%
2	Low-high	56%	37%
3	High	36%	21%

OS, overall survival; TR, Total response

1. 3. National comprehensive cancer network IPI scoring (NCCN-IPI)

This is produced from data from 1650 patients with de novo Diffuse large B-cell lymphoma treated at seven NCCN cancer centers between 2000 and 2010. The NCCN-IPI criteria are summarized in Table 16, and the survival times according to the NCCN-IPI scores are summarized in Table 17 [14].

Table 16. NCNN- IPI Scoring

Risk factors	Point
Age 61-60 61-75 >75	 1 2 3
ECOG ≥ 2	1
LDH > 1-3 > 3	 1 2
BM, CNS, Liver, GIT or lung involvement	1
Stage III or IV	1

BM, bone marrow; CNS, central nervous system; GIT, gastrointestinal tract

Table 17. Survival Time According to NCNN-IPI Scores

Score	Risk group	5-year PFS	5-year OS
0-1	Low	94%	96%

2-3	Low-medium	72%	77%
4-5	High-medium	54%	56%
≥ 6	High	35%	38%

OS, overall survival; PFS, progression-free survival

2. International Prognostic Index for Follicular Lymphoma (IPIFL)

FLIPI criteria:

1. Age >60 years
2. Serum LDH level, above normal
3. Hemoglobin level < 12 g/dL
4. Ann Arbor stage 3 or 4
5. Number of nodal involved areas >4

In the presence of the above criteria, each receives 1 point. In this way, patients receive a score between 0 and 5.

The survival times of 2192 follicular lymphoma patients diagnosed between 2004 and 2007, 68% of whom received rituximab, are presented in Table 18 according to the results obtained in the long-term survival study [15].

Table 18. International Prognostic Index for Follicular Lymphoma (IPIFL)

Score	Risk group	2-year PFS	2-year OS
0-1	Low risk	84%	98%
2	Medium risk	72%	94%
3 or more	High	65%	87%

OS, overall survival; PFS, progression-free survival

3. Mantle Cell Lymphoma International Prognostic Index (MIPI)

In MIPI scoring, patients receive a score between 0 and 12 (Table 19). Biological MIPI is determined by adding Ki-67 ratio to MIPI**.** The survival times of 455 patients diagnosed with Mantle cell lymphoma between 1996 and 2004, according to the MIPI scores

obtained in the long-term survival study, are given in Table 20 [16].

Table 19. Mantle Cell Lymphoma International Prognostic Index (MIPI)

Point	Age	Performance status (ECOG)	Serum LDH/ upper limit of normal	Leucocyte (10^9/L)
0	<50	0-1	<0.67	<6.7
1	50-59	-	0.67-0.99	6.7-9.9
2	60-69	2-4	1-1,49	10-14,9
3	≥ 70	-	≥1.5	≥15

ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; WBC, white blood count; MCL, mantle cell lymphoma; OS, overall survival

Table 20. Survival Time According to MIPI Scores

Score	Risk group	Median survival	5-year OS
0-3	Low risk	Not reached	60%
4-5	Medium risk	58 months	35%
6-12	High risk	37 months	20%

OS, overall survival; PFS, progression-free survival

4. International prognostic index (PIT) for peripheral T-cell lymphoma

1) Age: >60 years
2) LDH: High LDH
3) PS: >1 ECOG
4) Bone marrow involvement: positive

In the presence of the above criteria, each receives 1 point. Survival times according to PIT scores are given in Table 21 [17].

Table 21. Survival Time Acccording to PIT Scores

Point	5-year OS
0	62%
1	53%
2-3	33%
>3	18%

OS, overall survival

Follow-Up

Complete restaging should be performed at the end of treatment. Post-treatment PET/CT evaluation is recommended for aggressive lymphomas. Bone marrow aspiration and biopsy are repeated at the end of the treatment in cases with initial disease involvement. After the completion of the treatment, although depending on the patient-specific situation, follow-up is performed every 3 months for the first 2 years, every 6 months for the next 3 years, and then annually. As most relapses occur in the first 2 years after treatment, careful clinical evaluation during this time period is important to detect any signs of disease progression and relapse.

Frequently seen histopathological subtypes of NHL

1. B-cell lymphomas

1. 1. Small Lymphocytic Lymphoma (SLL)

It constitutes 4-5% of all lymphomas. It is CD5 (+) and CD23 (+), CD43 (+) and CD10 (-) . The lymphocyte count in blood should be <5000/μL. Detection of ZAP-70 by flow cytometry is an important prognostic marker. Hypogammaglobulinemia can be detected in 80% of cases. It can transform into the more aggressive Diffuse large B-cell lymphoma (Richter transformation) [2,4,5].

1. 2. Follicular Lymphoma

It consists of germinal center cells, often with a follicular growth pattern, with varying proportions of small centrocytes and large centroblasts. It constitutes 20-30% of lymphomas in western countries. Tumor cells often express surface immunoglobulin and CD10, as well as B-cell antigens (CD19, CD20, and CD22). Cells also show the CD5(-),

CD23(-), CD43(-) and CD11c (-) phenotype. Anti-apoptotic bcl-2 gene expression is present in 90-100% of patients. t(14;18) (q32;21) is seen in 80% of cases. Histopathological transformation is seen in 60–80% of patients with follicular lymphoma [2,4,5].

1. 3. Mantle cell lymphoma

It constitutes 5-8% of all lymphomas. It is more frequent in men and around the age of 60. Common disease is usually observed at the time of diagnosis. There may be Waldeyer's ring and bone marrow involvement. It may be together with extra-lymph node involvement, especially in the gastrointestinal tract (lymphomatous polyposis).

Tumor cells usually express IgM from surface immunoglobulins and often IgD together with B-cell antigens (CD19, CD20, CD22). Tumor cell phenotypes are CD5(+), CD10(-), CD23(-) and CD43(+).

The t(11:14) (q13;q32) (CCND1/BCL1 (11q13) gene, Ig heavy chain (IgH) (14q32) gene) translocation between the immunoglobulin heavy chain region and the bcl-1 region is detected in 70-100% of the cases. CCND1 gene overexpression develops secondary to this translocation. Overexpression of the PRAD1CCND1 gene causes overexpression of cyclin D1, which is a cell cycle regulatory protein. SOX11 (+) may be present in MHL cases [2,4,5].

1. 4. Marginal Zone Lymphoma (MZL)

Nodal marginal zone lymphoma (NMZL): The disease is characterized by lymph node involvement (limited or diffuse). Blood involvement is rare. In extranodal marginal zone lymphoma, most frequently the gastrointestinal tract (most often stomach) is involved. This is often followed by skin, salivary gland, lungs, orbit, thyroid, head and neck involvement. The area of involvement in splenic marginal zone lymphoma is the spleen. Some cases are hepatitis C virus positive and respond to antiviral therapy. In most cases, tumor cells carry surface immunoglobulin, cytoplasmic immunoglobulin, and B-cell antigens, but do not express CD5, CD10, CD23. Bcl-1 and bcl-2 gene rearrangements are not seen. t(11;18), t(1;14), t(14;18) and t (3;14) are associated with marginal zone lymphomas. Most patients with MALT lymphoma have a history of chronic antigen stimulation or autoimmune disease. Gastric MALT lymphoma is associated with Helicobacter pylori [2,4,5].

1. 5. Diffuse large B-cell lymphoma

It is the most frequently seen type of NHL. 60-65% of the cases have nodal onset, 35-40% have non-lymph node onset. For extranodal involvement, the gastrointestinal tract is most commonly involved, and they may be involvements of bone, central nervous system, kidney, and testis. Gastric involvement is most common in the gastrointestinal tract. Tumor cells frequently express surface and cytoplasmic immunoglobulin, B-cell antigens. Phenotypes can be CD20 (+), CD45 (±), CD5 (±) and CD10 (±). Bcl-2, Bcl-6, c-myc positivity can be seen in various combinations. According to positivity of these, they are called double-hit, tripple-hit lymphoma. Double-hit lymphoma includes cases of diffuse large B-cell lymphoma that show both myc and bcl-2 (and/or bcl-6) gene sequences with FISH. Double-hit lymphoma patients account for ≤10% of all diffuse large B-cell lymphoma cases. If both myc and bcl-2 (and/or bcl-6) are immunohistochemically demonstrated instead of FISH, it is named as double-expressive lymphoma [2,4,5].

1. 6. Primary mediastinal large B-cell lymphoma

It constitutes 7% of all diffuse large B-cell lymphoma cases. It is more common in middle-aged women. They often present themselves as a mass in the anterior mediastinum. Superior Vena Cava syndrome and airway compression are frequently seen [2,4,5].

1. 7. Burkitt Lymphoma

It is usually seen in children and young adults. It is seen more rarely in adults. It is an aggressive type of lymphoma that originates from B-cells. It is more common in men.

i) Endemic Burkitt lymphoma: It is common in Central Africa. It mostly starts from the jaw bones. EBV infection is found in 100% of cases.

ii) Sporadic Burkitt lymphoma: It occurs outside of Africa. Abdominal region (distal ileum, cecum or mesentery) involvement is common. EBV positivity is around 20%.

iii) AIDS-related Burkitt lymphoma: It is more common in adults.

The tumor consists of medium-sized monomorphic cells with a round nucleus, multiple nucleoli, and basophilic cytoplasm. Cytoplasmic lipid vacuoles and starry sky appearance are typical. Pathologically, starry sky appearance is very important in the lymph nodes. The tumor has a high proliferation rate due to increased mitosis and shows a high rate of spontaneous cell death. Therefore, spontaneous tumor lysis syndrome may develop.

Immunophenotypically, it expresses the B-cell antigens CD19, CD20, CD22 and CD10. Surface IgM is positive in cells. It is CD5(-) and CD 23(-). They express Bcl-6. In most of the cases, t(8;14) (q24;q32) (80%) translocation is observed as a result of translocation of the c-myc gene on chromosome 8 to the Ig heavy chain region on chromosome 14, t(8;22) (q24;q11) (15%) translocation is observed as a result of translocation of light chain lambda region in chromosome 22, and t(2;8) (q11;q24) (5%) translocation is observed as a result of translocation to the light chain kappa region in chromosome 2. Therefore, the c-MYC oncogene is positive in 100% of cases [2,4,5].

2. T-cell lymphomas

It constitutes 10-15% of all NHL cases.

2. 1. Peripheral T-Cell Lymphoma-NOS

It constitutes the vast majority of T-cell lymphomas. It constitutes 3.7% of all lymphomas. It is more common in men and over 60 years of age. Mainly, nodal involvement is typical, but extra-lymph node involvement can also be seen. They are often at an advanced stage at the time of diagnosis (Stage III/IV: 69%)
and bone marrow involvement is detected in 22% of the cases. Most cases have the CD4+/CD8 (–) phenotype. Loss of 9p, 5q, and 12q can be observed in 30% of cases [2,4,5].

2. 2. Angioimmunoblastic T-Cell Lymphoma

It constitutes 18-20% of T-cell lymphomas. Patients often present with B symptoms (68-85%) and diffuse lymphadenopathy (76-97%). Skin rash, ascites, hepatosplenomegaly, pleural effusion, arthritis, immunodeficiency, autoimmune events can be detected. At the time of diagnosis, 89% of the cases are at stage 3-4. Bone marrow involvement is detected in 29% of the cases. Anemia (40-57%), eosinophilia (39%), pancytopenia, and polyclonal hypergammaglobunemia may be seen [2,4,5].

2. 3. Anaplastic large cell lymphoma

It constitutes 2-8% of all lymphomas. The anaplastic lymphoma kinase (ALK) gene is divided into two subgroups as positive and negative. The majority express CD30. Clinical symptoms sometimes differ little from mediastinal Hodgkin's disease with large tumor masses. In these cases, it is quite difficult to diagnose. However, they show CD15 (-) properties. ALK+ anaplastic large cell lymphoma is more common in men and in the first 30 years of life. Most patients present with disease at stage 3-4 and B symptoms. It expresses

T-cell antigens at varying rates. The most common genetic change is t(2,5) (p23;q35) (50%). ALK (+) Anaplastic large cell lymphoma shows better prognostic features [2,4,5].

2. 4. Lymphoblastic Lymphoma

It is more frequently seen in childhood and adolescence. It is mostly of T-cell origin (80-90%). They usually present with a rapidly growing mediastinal tumor. Pleural effusion and superior vena cava syndrome may be seen due to mediastinal mass. Bone marrow infiltration and leukemic transformation develop in 60% of cases. Bone marrow and nervous system infiltration indicates a poor prognosis. Mitoses are common. Tumor lysis syndrome may be seen. T-cell phenotype (CD7+, CD3+, CD1a+, TdT+) predominates in tumors [2,4,5].

RESOURCES

1. PDQ Adult Treatment Editorial Board. Adult Non-Hodgkin Lymphoma Treatment (PDQ®): Health Professional Version. April 20, 2018.
2. Hoffbrand AV, Higgs DR, Keeling DM, Mehta AB. Postgraduate Hematology, 7 th edition, Wiley Blackwell; 2016, p.669-758.
3. https://hsgm.saglik.gov.tr/depo/birimler/kanser-db/istatistik/Trkiye_Kanser_statistikleri-2015.pdf (Accessed on June 29, 2020.)
4. Hoffman R, Silberstein L, Heslop HE, Weitz JI, Anastası J, eds. Hematology Basic Principles and Practice, 6 th ed. Philadelphia: Elsevier Saunders;2013.p.1112-1303.
5. Armitage JO, Mauch PM, Harris NL, eds. Non-Hodgkin Lymphomas, 2nd ed., Philedelphia: Wolters Kluwer/Lippincott Williams and Wilkins;2010.p.196-373.
6. Diumenjo MC, Abriata,G, Forman D, Sierra MS. Etiology of non-Hodgkin lymphoma in Central and South America. In: Cancer in Central and South America. Lyon: International Agency for Research on Cancer; 2016 (https://gco.iarc.fr/resources.php, accessed on June 30, 2020.)
7. Swerdlow SH, Campo E, Stefano A, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Blood. 2016;127(20):2375-2390.
8. Arber DA, Orazi A, Hasserjian R, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood. 2016; 127(20):2391-2405.
9. Armitage JO, Weisenburger DD. New approach to classifying non-Hodgkin's lymphomas: clinical features of the major histologic subtypes. Non-Hodgkin's Lymphoma Classification Project. *J Clin Oncol*. 1998;16(8):2780-2795. doi:10.1200/JCO.1998.16.8.2780
10. Harris NL, Jaffe ES, Diebold J, et al. World Health Organization classification of neoplastic

diseases of the hematopoietic and lymphoid tissues: Report of the Clinical Advisory Committee meeting-Airlie House, Virginia, November 1997. J Clin Oncol 1999; 17:3835.

11. Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: The Lugano classification. J Clin Oncol 2014; 32(27):3059-67.
12. Ziepert, M, Hasenclever, D, Kuhnt, E, et al. Standard International Prognostic Index remains a valid predictor of outcome for patients with aggressive CD20+ B-cell lymphoma in the rituximab era. J Clin Oncol 2010; 28:2373.
13. The International Non-Hodgkin's Lymphoma Prognostic Factors Project. N Engl J Med 1993; 329:987.
14. Zhou Z, Sehn LH, Rademaker AW, et al. An enhanced International Prognostic Index (NCCN-IPI) for patients with diffuse large B-cell lymphoma treated in the rituximab era. Blood 2014; 123:837.
15. Nooka AK, Nabhan C, Zhou X, et al. Examination of the follicular lymphoma international prognostic index (FLIPI) in the National LymphoCare study (NLCS): a prospective US patient cohort treated predominantly in community practices. Ann Oncol 2013; 24:441.
16. Hoster E, Dreyling M, Klapper W, et al. A new prognostic index (MIPI) for patients with advanced-stage mantle cell lymphoma. Blood 2008; 111:558.
17. 17.Piccaluga PP, Agostinelli C, Gazzola A, et al. Prognostic Markers in Peripheral T-Cell Lymphoma. Curr Hematol Malig Rep (2010) 5:222–228.

2.11. Ovarian Cancers

Epithelial Ovarian-Tube-Peritoneal Cancer

Ovarian cancer is one of the leading causes of death due to gynecological malignancies in our country. 95% of ovarian malignancies are of epithelial origin, and the remaining partial are germ cell tumors and sex cord stromal tumors arising from other ovarian cells. The annual incidence of new epithelial ovarian-tubaperitoneal cancer in Turkey is 6.4/100,000 according to 2016 data[1]. The incidence of epithelial ovarian-tube-peritoneal cancer increases with age and is most frequently observed between the ages of 50-70. The average age of onset is 63 years, and 70% of patients are at stage 3C and above at the time of diagnosis [2].

Epidemiology

Worldwide, 225,000 new cases of ovarian cancer and 140,000 deaths due to ovarian

cancer were reported in 2008 [3]. US National Cancer Database Surveillance, Although there are racial differences according to the data of Epidemiology and End Results (SEER), the annual incidence of ovarian cancer is given as 10/100000 [4]. According to the data of the same institution, the lifetime risk of ovarian cancer has been reported as 1.4%.

Risk Factors

1. Uninterrupted Ovulation: Repetitive continuous ovulation causes minor trauma on the ovarian epithelium and this increases the incidence of epithelial ovarian cancer. [5].
2. Gonadotropin exposure: Chronic exposure of the ovaries to gonadotropin and increased oestrogen concentration are considered carcinogenic [6].
3. Age: The incidence of epithelial ovarian cancer increases with increasing age. According to the American Nurses' Health Study (NHS), the risk of developing epithelial ovarian cancer increases by 2% with one year of increase in age below the age of 50, and by 11% with one year of increase in age after the age of 50 [6].
4. Nulliparity: The risk of encountering epithelial ovarian cancer is increased in nulliparous women. [7].
5. Early menarche-Late menopause: Some studies have shown that the risk of epithelial ovarian cancer increases with early menarche [8].
6. Endometriosis: It has been shown that there is an increase in the frequency of ovarian cancer due to certain histological types together with endometriosis. In a meta-analysis including 8,000 women, it is seen that the risk of clear cell carcinoma, endometrioid carcinoma, and low-grade serous carcinoma has increased. (10-11)
7. Polycystic ovary syndrome: According to a meta-analysis of 8 studies, there is a statistically significant increase [12].
8. Genetic causes: Many ovarian cancer-related genes have been identified. BRCA1, BRCA2, BRIP1, RAD51C, RAD51D, mismatch repair genes (Lynch syndrome) have a role in the development of epithelial ovarian cancer. The lifetime risk of ovarian cancer varies between 20% and 60% in BRCA1 mutations (13, 14, 15). Ovarian cancers due to BRCA mutations are not frequently seen before the age of 40. Ovarian cancer due to BRCA1 mutation is seen around the age of 54, and ovarian cancer due to BRCA2 mutation is seen around the age of 62 (16). BRCA-associated ovarian cancers are often epithelial and mostly in high-grade serosis and

undifferentiated histology (17, 18, 19, 20, 21). Hereditary non-polyposis colorectal cancer (HNPCC) syndrome, also known as Lynch syndrome, is autosomal dominant inherited. This hereditary cancer syndrome is accompanied by colorectal, gastric, hepatobiliary, endometrial, ovarian and genitourinary system cancers. Lynch syndrome is caused by damage to one of the DNA mismatch repair genes. These genes are MLH1, MSH2, MSH6 and PMS2 (22, 23, 24). Ovarian cancers due to Lynch syndrome, on the other hand, mostly have endometrioid and clear cell histology. Studies have shown that the incidence of ovarian cancer in individuals with BRIP1, RAD51C, RAD51D, PALB2, and BARD1 gene mutations increases between 5 and 12 times compared to the normal population (25).

9. Smoking: While smoking leads to an increase in mucinous type among epithelial ovarian cancers, it does not cause an increase in other histological types (26).
10. Talc-Asbestos: Although there is a limited source showing an increase in the development of epithelial ovarian cancer due to the use of talcum powder and asbestos, there is a meta-analysis including 16 studies showing the development of epithelial ovarian cancer in the use of perineal talcum powder (27).
11. Obesity: There is a relationship between high body mass index and ovarian cancer, although this relationship is not very strong. In a review including 28 studies, the risk of developing ovarian cancer was found to be 1.3 in patients with a BMI of 30 kg/m2 and above (28).

Histological Subtypes

Although there are basically 4 subtypes of ovarian-tube-peritoneal cancer (serous, endometrioid, clear cell, mucinous), serous cell carcinoma is the most frequently seen one. According to the 2016 NCCN recommendations, high-grade serous and endometrioid carcinoma mucinosis are managed differently from clear cell and low-grade endometrioid carcinoma. Serous carcinomas are defined as high-grade and low-grade. While high-grade serous carcinomas are tumors responsive to chemotherapy, but with a poor prognosis, low-grade serous carcinomas are tumors unresponsive to chemotherapy, with a good prognosis.

Approach to a Suspicious Ovarian-Tube-Peritoneal Cancer Case

Surgical exploration is often needed for diagnosis in patients with ovarian-tube-peritoneal cancer. Especially in early stage patients, removal of the tumor without fragmentation is very important as it will prevent the stage progression of the patient. Therefore, ovarian biopsy is not a recommended method to define the disease. Paracentesis,

thoracentesis, or tissue biopsies can be performed prior to neoadjuvant chemotherapy in patients who are unsuitable for surgical staging (due to tumor extent or overall performance). Suspicion of an adnexal mass and showing it with imaging is the most important part of the evaluation. Symptoms, laboratory findings, and risk factors are the findings that support the clinical suspicion of malignancy. Transvaginal-transabdominal USG, abdominopelvic tomography or magnetic resonance imaging can be used to define an adnexal mass. CA 125, HE4, CA19-9, Ca 15-3 can be used as tumor markers initially. CEA can be used to eliminate adnexal metastasis of colon cancer, and inhibin, LDH, hcg ve AFP can be used to eliminate other tumors of ovarian origin (germ cell-sex cord stromal). Preoperative evaluation should be performed in patients with suspected ovarian-tube-peritoneal tumor based on clinical examination, symptoms, tumor markers, and imaging. During this evaluation, the patient's tolerance to staging surgery and the extent of the tumor should be evaluated. If the patient will not benefit from a possible staging surgery, histopathological identification should be made by taking a biopsy from the tumoral tissue.

Surgical Staging

Ovarian-tube-peritoneal cancer is staged by 2013 staging system of the International Federation of Gynecology and Obstetrics (FIGO) [29]. With this staging system, ovarian, tubal and peritoneal cancers are staged in the same way, and there is no difference in staging between histopathological subtypes. Total extrafacial hysterectomy, bilateral salpingo-oophorectomy, pelvic and paraaortic lymph node dissection, infracolic or infragastric omentectomy, abdominal lavage sampling are the standard staging surgical procedures of ovarian-tubal-peritoneal cancer. Evaluation of the upper abdomen, all peritoneal surfaces, small-large bowel mesentery should be added to the procedure. Appendectomy can also be added to the procedure. Although laparotomy is generally used, laparoscopy can also be applied in very special cases (Table 22).

Primary Treatment

1. **Neoadjuvant Chemotherapy**

Neoadjuvant chemotherapy is the administration of systemic therapy before definitive surgery. Neoadjuvant chemotherapy is aimed to reduce perioperative morbidity and mortality and increase the rates of complete resection at the time of surgery. Although it has not been clearly determined which patient group should be given neoadjuvant

chemotherapy, neoadjuvant chemotherapy is a treatment method that can only be applied in patients with advanced-stage ovarian cancer (Stage 3c-4b). The first criterion in patient selection for neoadjuvant chemotherapy is the evaluation of the patient's performance. If the patient cannot tolerate primary cytoreductive surgery with her comorbid conditions, she is a suitable candidate for neoadjuvant chemotherapy. The second criterion is that neoadjuvant chemotherapy should be considered if there is a tumor in areas that cannot be surgically resected. Computed tomography, magnetic resonance, PET and, if necessary, diagnostic laparoscopy can be used to identify these regions [30].

2. Primary Cytoreductive Surgery

Surgical cytoreduction is together with increased survival in ovarian tubal peritoneal cancer. The amount of residual tumor after cytoreductive surgery is inversely related to survival [31]. The aim is to operate in such a way that there is no residual disease after surgical cytoreduction [32].

- **Complete cytoreduction:**There is no visible disease
- **Optimal cytoreduction:** Residual disease up to 1cm
- **Suboptimal cytoreduction:** Residual tumor larger than 1 cm

In a systemic review of 11 retrospective studies, the mean survival rate in optimally operated patients (1 cm) was found to be statistically significantly higher. In the same study, patients with complete cytoreduction (no tumor) had a statistically significant increase in survival compared to patients with optimal cytoreduction (<1 cm tumor) [33].

Despite the survival advantage, cytoreduction can be associated with significant morbidity and potential delays in starting chemotherapy. Long-term hospitalizations and delays in starting chemotherapy can be seen in these patients [34].

3. Interval Cytoreduction

It is cytoreductive surgery applied after an average of 4 cycles of chemotherapy, in patients treated with neoadjuvant chemotherapy. Patients who respond to neoadjuvant chemotherapy or have the stable disease are candidates for interval cytoreduction. The surgical procedure in interval cytoreduction is similar to primary cytoreduction and includes the same rules. For maximal cytoreduction, the maximal target should be spent, any suspicious peritoneal involvement should be excised.

Chemotherapy

After completing their surgical treatment, patients with ovarian cancer have to undergo chemotherapy in all stages, except Stage 1A and 1B. As initial therapy, they receive 6 cycles of Paclitaxel (Taxol) + Carboplatin every 3 weeks. If the imaging tests and tumor marker measurements at the end of the treatment are normal, the treatment is discontinued and the patients are followed every 3 months for the first 2 years, and every 6 months for the second 2 years if everything is normal, and then once a year for life.

RESOURCES

1. T.R. Ministry of Health TPHI Turkey Cancer Statistics. 2019.
2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. CA Cancer J Clin. 2016 Jan-Feb;66(1):7-30. doi: 10.3322/caac.21332. Eprub 2016 Jan 7
3. Jemal A, Bray F, Center MM, et al. Global cancer statistics. CA Cancer J Clin 2011; 61:69.
4. http://seer.cancer.gov/statfacts/html/ovary.html (Accessed on April 24, 2012)
5. Salehi F, Dunfield L, Phillips KP, et al. Risk factors for ovarian cancer: an overview with emphasis on hormonal factors. J Toxicol Environ Health B Crit Rev 2008; 11:301.
6. Kammerman S, Demopoulos RI, Ross J. Gonadotropin receptors in experimentally induced ovarian tumors in mice. Cancer Res 1977; 37:2578.
7. Stewart LM, Holman CD, Aboagye-Sarfo P, et al. In vitro fertilization, endometriosis, nulliparity and ovarian cancer risk. Gynecol Oncol 2013; 128:260.
8. Sueblinvong T, Carney ME. Current understanding of risk factors for ovarian cancer. Curr Treat Options Oncol 2009; 10:67.
9. Tsilidis KK, Allen NE, Key TJ, et al. Oral contraceptive use and reproductive factors and risk of ovarian cancer in the European Prospective Investigation into Cancer and Nutrition. Br J Cancer 2011; 105:1436.
10. Pearce CL, Templeman C, Rossing MA, et al. Association between endometriosis and risk of histological subtypes of ovarian cancer: a pooled analysis of case-control studies. Lancet Oncol 2012; 13:385.
11. Van Gorp T, Amant F, Neven P, et al. Endometriosis and the development of malignant tumours of the pelvis. A review of literature. Best Pract Res Clin Obstet Gynaecol 2004; 18:349.
12. Chittenden BG, Fullerton G, Maheshwari A, Bhattacharya S. Polycystic ovary syndrome and the risk of gynaecological cancer: a systematic review. Reprod Biomed Online 2009; 19:398.

13. Struewing JP, Hartge P, Wacholder S, et al. The risk of cancer associated with specific mutations of BRCA1 and BRCA2 among Ashkenazi Jews. J Natl Cancer Inst Monogr 1995; 17:33–5.
14. Aziz S,Kuperstein G,Rosen B,et al.A Genetic Epidemiological Study of Carcinoma of the Fallopian Tube.Gynecol Oncol 2001;80:341-345
15. Levine DA,Argenta PA,Yee CJ et al.Fallopian Tube and Primary Peritoneal Carcinomas Associated With BRCA Mutations.J Clin Oncol 2003;21:4222-4227
16. Boyd J, Sonoda Y, Federici MG, et al: Clinicopathologic features of BRCAlinked and sporadic ovarian cancer. JAMA 283:2260-2265, 2000
17. Evans DGR, Young K, Bulman M, et al. Probability of BRCA1/2 mutation varies with ovarian histology: results from screening 442 ovarian cancer families. Clin Genet 2008; 73:338–45.
18. Lakhani SR, Manek S, Penault-Llorca F, et al. Pathology of ovarian cancers in BRCA1 and BRCA2 carriers. Clin Cancer Res 2004; 10:2473–81
19. Pal T, Permuth-Wey J, Betts JA, et al. BRCA1 and BRCA2 mutations account for a large proportion of ovarian carcinoma cases. Cancer 2005; 104:2807–16.
20. Risch HA, McLaughlin JR, Cole DE, et al. Prevalence and penetrance of germline BRCA1 and BRCA2 mutations in a population series of 649 women with ovarian cancer. Am J Hum Genet 2001; 68:700-10
21. Shaw PA, McLaughlin JR, Zweemer RP, et al. Histopathologic features of genetically determined ovarian cancer. Int J Gynecol Pathol 2002; 21:407–11.
22. Rebbeck TR et al (2005) Effect of short-term hormone replacement therapy on breast cancer risk reduction after bilateral prophylactic oophorectomy in BRCA1 and BRCA2 mutation carriers: the PROSE Study Group. J Clin Oncol 23(31):7804–7810
23. Lu KH et al (2000) Occult ovarian tumors in women with BRCA1 or BRCA2 mutations undergoing prophylactic oophorectomy. J Clin Oncol 18(14):2728– 2732
24. Aarnio M, Sankila R, Pakkula E, et al: Cancer risk in mutation carriers of DNA-mismatch repair genes. Int J Cancer 81:214-218, 1999
25. Song H, Dicks E, Ramus SJ, et al. Contribution of Germline Mutations in the RAD51B, RAD51C, and RAD51D Genes to Ovarian Cancer in the Population. J Clin Oncol 2015; 33:2901
26. Jordan SJ, Whiteman DC, Purdie DM, et al. Does smoking increase risk of ovarian cancer? A systematic review. Gynecol Oncol 2006; 103:1122.
27. Gates MA, Rosner BA, Hecht JL, Tworoger SS. Risk factors for epithelial ovarian cancer by histologic subtype. Am J Epidemiol 2010; 171:45.
28. Olsen CM, Green AC, Whiteman DC, et al. Obesity and the risk of epithelial ovarian cancer:

a systematic review and meta-analysis. Eur J Cancer 2007; 43:690.

29. Prat J, FIGO Committee on Gynecologic Oncology. Staging classification for cancer of the ovary, fallopian tube, and peritoneum. Int J Gynaecol Obstet 2014; 124:1.
30. Vergote I, du Bois A, Amant F, et al. Neoadjuvant chemotherapy in advanced ovarian cancer: On what do we agree and disagree? Gynecol Oncol 2013; 128:6.
31. Bristow RE, Tomacruz RS, Armstrong DK, et al. Survival effect of maximal cytoreductive surgery for advanced ovarian carcinoma during the platinum era: a meta-analysis. J Clin Oncol 2002; 20:1248
32. Chang SJ, Hodeib M, Chang J, Bristow RE. Survival impact of complete cytoreduction to no gross residual disease for advanced-stage ovarian cancer: a meta-analysis. Gynecol Oncol 2013; 130:493.
33. Elattar A, Bryant A, Winter-Roach BA, et al. Optimal primary surgical treatment for advanced epithelial ovarian cancer. Cochrane Database Syst Rev 2011;: CD007565.
34. Wright JD, Herzog TJ, Neugut AI, et al. Effect of radical cytoreductive surgery on omission and delay of chemotherapy for advanced-stage ovarian cancer. ObstetGynecol 2012; 120:871

Table 22. FIGO Stage in Epithelial Overian-Tube-Peritoneal Cancers (2013)

Stage IA	Tumor limited to one ovary; capsule intact, no tumor on ovarian surface, negative
Stage IB	Tumoral involvement on both ovaries in the Stage 1 a features
Stage IC	Tumor limited to one or both ovaries
Stage 1CI	Surgical spill
Stage 1C2	Capsule ruptured before surgery, tumor on ovarian surface
Stage 1C3	Malignant cells in ascites or peritoneal fluid
Stage IIA	Spread or implants on the uterus or fallopian tubes
Stage IIB	Spread in other intraperitoneal pelvic tissues except uterus and fallopian tubes
Stage IIIA	Tumor limited to positive retroperitoneal lymph node or pelvis microscopic metastasis
Stage IIIA1	Positive retroperitoneal lymph nodes
Stage IIIA1i	Lymph nodes ≤10 mm
Stage IIIA1ii	Lymph nodes ≤10 mm
Stage IIIA2	Microscopic peritoneal metastasis beyond the pelvis with or without positive retroperitoneal lymph nodes
Stage IIIB	Macroscopic peritoneal metastasis beyond the pelvis <2 cm with or without positive retroperitoneal lymph nodes including extension to liver or spleen capsule
Stage IIIC	Macroscopic peritoneal metastasis beyond the pelvis >2 cm with or without positive retroperitoneal lymph nodes including involvement to liver capsule or spleen
Stage IVA	Pleural effusion with positive cytology
Stage IVB	Liver or spleen parenchymal metastases; metastases to extra-abdominal organs (including inguinal lymph nodes and lymph nodes outside the abdominal cavity)

2.12. Laryngeal Cancer

Epidemiology:

Head and neck cancers are the cause of more than 650,000 cases and 330,000 deaths annually worldwide [1]. In the United States, head and neck cancers account for approximately 3 percent of all cancers [2]. Head and neck cancers are more common in men than in women, at a ratio of 4:1 or 2:1, with regional differences. Laryngeal carcinoma is the most frequently seen subgroup of head and neck cancers and constitutes 1% to 5% of all cancers.[3] It is the 11th most common form of cancer among men worldwide [4]. While laryngeal cancer is seen at a rate of 5.8 per 100,000 men, it is seen at a rate of 1.2 per 100,000 women [5]. With 6916 cases reported between 2012 and 2016 in our country, it is the 9th most common cancer in men, but is not among the top 10 cancers in women [6]. The distribution of laryngeal cancer varies according to racial and geographical differences; it is observed 50% more frequently in Afroamerican race [7]. In addition, it has been observed that the mortality of laryngeal cancer is higher in the Afroamerican race, where the incidence of Human Papilloma Virus (HPV) is low [8].

Risk Factors

Chemical carcinogenesis, which occurs as a result of exposure to environmental carcinogens, plays an important role in the formation of laryngeal cancer. Tobacco products, including cigarettes, are the most accused agent in the etiology of laryngeal cancer. In studies, it is reported that approximately 97% of patients with laryngeal cancer smoke [9,10]. When smokers and non-smokers are compared, it is found that the risk of laryngeal cancer is 30 times higher in those who smoked half a pack of cigarettes for at least 10 years [11]. It has also been shown that in smokers the risk of laryngeal cancer increases as the amount of smoking increases, depending on the dose [12]. It has been shown that the risk rate decreases in those who quit smoking, and that, in the group with heavy smoking, the risk of laryngeal cancer decreases from 13.4 times to 3 times after 10-year cessation period and 2.5 times after 16-year cessation period [11,12]. For laryngeal cancer, smoking tobacco has been shown to be 7-10 times more carcinogenic than chewing it [13].

Alcohol consumption is another important risk factor for the formation of laryngeal cancer. In studies, it is reported that the risk of laryngeal cancer increases 4-22 times with

alcohol consumption [12,14]. Generally, in head and neck cancers, when those who drink alcohol above 50 g/day are compared with those who drink less than 10 g/day, a higher risk of cancer was observed in the group with high alcohol consumption [15]. The higher the amount of alcohol consumed, the higher the risk of laryngeal cancer.

It is known that HPV is involved in the etiology of head and neck tumors. HPV causes laryngeal cancer by suppressing the tumor suppressor gene p53 with the E6 protein it produces [16]. In a meta-analysis of 148 studies, the prevalence of HPV in laryngeal cancer was 22%, with HPV type 16 being the most common [17]. HPV positive cases had a better prognosis compared to negative cases [8,18].

The incidence of laryngeal cancer increases in solid organ transplant recipients and those with immunodeficiency [19]. It is known that occupational exposure to substances such as asbestos cement dust, tar and wood dust increases the risk of laryngeal cancer 1.5-5.1 times [13,20]. In general, the protective effect of vegetable and fruit consumption from head and neck cancers was observed, and the level of vitamin A was found to be low in patients with head and neck tumors. Head and neck squamous cell carcinoma were found to be 2-3 times higher in vitamin A and C deficiencies [21]. It has also been observed that the risk of laryngeal cancer increases in patients with poor oral hygiene, periodontal disease, gastroesophageal reflux disease, or exposure to radiation [22-24].

Cigarette and alcohol consumption are the most important environmental factors in laryngeal cancer. They show a synergistic effect on each other. By avoiding these two risk factors, a serious reduction in the risk of laryngeal cancer can be achieved, similar to many other tumor types.

Clinic, Diagnosis and Staging

The larynx consists of three parts, namely supraglottic, glottic, and subglottic. 60-65% of laryngeal cancers are sourced from glottic, 30-35% from supraglottic, and 5% from infraglottic. Symptoms associated with laryngeal cancer depend on the site of involvement. While persistent hoarseness may be the main complaint in glottic cancers, symptoms such as dysphagia, chronic cough, hemoptysis, and stridor may be observed clinically. Supraglottic cancers are generally diagnosed later than glottic tumors. Supraglottic cancers are usually diagnosed with airway obstruction or palpable metastatic lymph nodes. Primary

subglottic tumors are rare. Affected patients usually present with exertional dyspnea. Since glottic tumors give symptoms before they do not spread to regional lymph nodes, with hoarseness, they are often diagnosed at an early stage. Therefore, glottic tumors have an excellent cure rate of 80-90%. In contrast, as supraglottic tumors have richer lymphatic drainage, they spread to regional lymph nodes. Therefore, at diagnosis supraglottic cancer is usually a locally advanced disease.

Initial evaluation of the primary tumor should be made with a combination of a comprehensive history and examination, palpation, indirect mirror examination, and direct flexible laryngoscopy. In tumor evaluation, regional lymph nodes should be carefully evaluated and patients, especially those with tobacco and alcohol use, with lymph node involvement should be evaluated for metastatic disease and second primary lung cancer. Especially for laryngeal tumors, an examination, usually under anesthesia, is performed to best characterize the size of the tumor, search for synchronous secondary primary tumors and take biopsies for tissue diagnosis. In general, in patients with a history of heavy alcohol or tobacco use, an extra study is recommended for second primary tumors with PET or panendoscopy as part of staging to characterize the primary tumor or look for distant disease in early stage disease. The most common distant metastases of head and neck tumors are lung, liver and bone. The second primary sites are the head and neck, lung, and esophagus. Therefore, imaging studies should be done to include them.

Fine needle aspiration biopsy from tissue or metastatic lymph node is often used for the pathological diagnosis of the tumor. This technique has high sensitivity and specificity [25,26]. Another promising strategy to improve the accuracy of overall staging is sentinel lymph node biopsy [27–30]. This procedure is usually done at the same time as surgical resection of the tumor. Like cutaneous melanoma, this technique also uses preoperative lymphoscintigraphy, intraoperative blue dye and a hand-held gamma probe. Sentinel lymph node biopsy is a reliable and reproducible method for the clinical and radiological staging of N0 disease in head and neck tumors. It can also be used to identify patients with midline malignancies, positive ipsilateral lymph nodes and clinically negative contralateral neck lymph nodes.

Imaging studies (CT, magnetic resonance imaging [MRI], PET, and integrated PET/CT) are important to evaluate the degree of local invasion, involvement of regional

lymph nodes and the presence of distant metastases or second primary tumors.

The eighth edition (2017) of the tumor, node, metastasis (TNM) system is used for staging. Generally, stage I or II disease is described by a relatively small (T1 and T2 tumors) primary tumor without nodal involvement. Stage III or IV cancers usually contain larger primary tumors that may invade neighboring structures and/or spread to regional lymph nodes. As the stage progresses, the prognosis of the disease worsens.

Treatment

Treatment of laryngeal cancer requires a multimodal approach that includes surgery, radiotherapy (RT) and chemotherapy (CT). Endoscopic resection, laser or radiotherapy may be preferred for the treatment of carcinoma in situ [31,32].

A systematic review published in 2009 showed that surgery or radiotherapy had similar efficiency for early-stage glottic or supraglottic cancers [33]. Also in a meta-analysis of 48 studies about T2 tumors, the 5-year local control rates of transoral surgery and radiotherapy were similar [34]. The choice of treatment method depends on the expected functional outcome, patient's wishes, reliability of follow-up and general medical condition [35]. If it is to be treated by primary surgery, total laryngectomy is recommended. For locally advanced disease with good performance status, the combined use of chemotherapy and radiotherapy in the functional organ-preserving approach has replaced total laryngectomy plus radiotherapy. However, conservative surgical techniques can be used to preserve vocal cord functions in selected patient groups. Pulmonary functions should be evaluated before surgery. Adjuvant therapy depends on the presence or absence of adverse features. For T1-2 N0 patients, adjuvant therapy can be applied in a well-selected patient group who underwent re-resection with surgical margins positivity.

Resectable, advanced glottic or supraglottic laryngeal cancers are usually managed with a combined modality approach. While total laryngectomy can be performed in this group, if laryngeal protection can be performed, concomitant systemic therapy with radiotherapy is recommended according to the results of the Intergroup trial RTOG 91-11 [36,37]. The Intergroup trial RTOG 91-11 study was consisting of 3 arms: the first arm was induction radiotherapy after three cycles of CF (cisplatin + 5-fluorouracil), and the second arm was cisplatin concurrent radiotherapy and the third arm was radiotherapy alone. The radiotherapy dose given in all 3 arms was similar. Two-year local disease control was

statistically significantly superior to the concurrent cisplatin arm (88%), induction chemotherapy arm (74%) and radiotherapy alone (69%). In light of these results, concomitant chemoradiotherapy was defined as a treatment option to obtain laryngeal protection for T3N0 and node-positive supraglottic cancers and at most T3 glottic cancers and any N-positive glottic cancers. While similar results were obtained in the 10-year results of this study, no difference was observed between the three arms in terms of 10-year survival. However, non-cancer deaths were higher in the chemoradiotherapy arm [36]. Based on the long-term update of RTOG 91-11, induction chemotherapy remains to be an option for patients requiring total laryngectomy other than T1-2N0 [36]. For patients with laryngeal cancer, after complete or partial response with induction chemotherapy, RT alone is recommended (category 1), while chemoradiotherapy (category 2B recommendation) may also be administered after partial response [36–40]. In the phase II TREMPLIN study, induction in patients with laryngeal and hypopharyngeal cancer was sequentially divided into RT+Cisplatin and RT+Cetuximab arms after three cycles of chemotherapy [41]. Local control was superior in the cisplatin arm, but laryngeal protection, laryngeal function, and overall survival were similar for the two treatment groups in the cisplatin and cetuximab arms (95% vs. 93%, 87% vs. 82%, and 89% vs. 92%, respectively). As a result of this study, it was observed that the administration of cisplatin together with RT to patients receiving cisplatin in induction therapy significantly increased the toxicity, whereas Cetuximab may be an option for patients who are not suitable for taking platinum. In definitive radiotherapy and anti-EGFR targeted therapy, cetuximab may be an option for patients who are unsuitable or unwilling for systemic chemotherapy.

The recommended treatment approach for patients with glottic and supraglottic T4a tumors is total laryngectomy with thyroidectomy and neck dissection (depending on node involvement), followed by adjuvant therapy (RT or systemic therapy/RT) [42].

In metastatic laryngeal carcinoma, response rates of single-agent chemotherapy range from 15 to 35% [43–45]. In addition to commonly used agents such as cisplatin, carboplatin, and taxanes as a single agent, cetuximab, which is effective on EGFR, is expressed at a rate of 90% in squamous cell non-nasopharyngeal head and neck tumors, can be used alone or in combination with platinum. Responses obtained with the combined regimens are better. A phase III randomized trial of 442 patients with relapsed or metastatic squamous cell carcinoma (EXTREME) showed that cetuximab+cisplatin/5-FU or carboplatin/5-FU

improved median survival compared with standard systemic doublet chemotherapy [46]. In general, it is recommended to add 5-FU and cetuximab to cisplatin or caboplatin at category 1 in non-nasopharyngeal metastatic squamous cell head and neck tumors. Alternatively, platinum+taxane, cisplatin+cetuximab, cisplatin+5-FU, and platinum+taxane+cetuximab can be used [46-50].

RESOURCES

1. Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018; 68:394.
2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. CA Cancer J Clin 2020; 70:7.
3. Le HJ, Chen SY, Li Y et al. 2019;33(11):1017-1021. doi: 10.13201/j.issn.1001-1781.2019.11.003
4. National Cancer Institute, US National Institutes of Health. Surveillance, Epidemiology, and End Results (SEER) Program, Cancer Statistics Branch, released April 2007, based on the November 2006 submission
5. Baselga J. Why the epidermal growth factor receptor? The rationale for cancer therapy. *Oncologist*. 2002; 7(suppl 4): 2– 8.
6. T.R. Ministry of Health General Directorate of Public Health Turkey cancer statistics 2016
7. DeSantis C, Naishadham D, Jemal A. Cancer statistics for African Americans, 2013. CA Cancer J Clin 2013; 63:15
8. Settle K, Posner MR, Schumaker LM, et al. Racial survival disparity in head and neck cancer results from low prevalence of human papillomavirus infection in black oropharyngeal cancer patients. Cancer Prev Res (Phila) 2009; 2:776
9. Maier, H., Gewelke, U., Dietz, A., & Heller, W.-D. (1992). Risk Factors of Cancer of the Larynx: Results of the Heidelberg Case—Control Study. *Otolaryngology–Head and Neck Surgery*, *107*(4), 577–582.
10. DeStefani E, Correa P,Orregia F, et al. Risk Factors for laryngeal cancer. Cancer 1987: 60: 3087-3091
11. Wyncler EL, Bross IJ, Day E. A study of the environmental factors in cancerof the larynx. Cancer 1956: 9: 89-110
12. Falk RT, Pickle LW, Brown LM et al. Effect of smoking and alcohol consumption on laryngeal cancer risk in coastal Texas. Cancer Res 1989: 49: 4024-4029.
13. Jayant K**,** Balakrishman V, Sanghvi LD, et al. Carcinoma of the nose and paranasal sinuses in woodworkers in the state of Victoria Australia. Cancer 1975; 36: 1115-1121.

14. Koufman JA. The otolaryngologic manifestaions of gastroesophageal reflux disease. Laryngoscope 1991; 10 (supp 53): 1-78.
15. De Stefani E, Boffetta P, Oreggia F, et al. Hard liquor drinking is associated with higher risk of cancer of the oral cavity and pharynx than wine drinking. A case-control study in Uruguay. Oral Oncol 1998; 34:99.
16. Salam MA, Rockett J, Morris A. General primer-ediated polymerase chain reaction for simultaneous detection and typing of human papillomavirus DNA in laryngeal sqoamous cell carcinomas. Clin Otolaryngol 1995; 20: 84-88.
17. Ndiaye C, Mena M, Alemany L, et al. HPV DNA, E6/E7 mRNA, and p16INK4a detection in head and neck cancers: a systematic review and meta-analysis. Lancet Oncol 2014; 15:1319
18. Tian S, Switchenko JM, Jhaveri J, et al. Survival outcomes by high-risk human papillomavirus status in oropharyngeal head and neck squamous cell carcinomas: A propensity-scored analysis of the National Cancer Data Base. Cancer 2019; 125:2782.
19. Rabinovics N, Mizrachi A, Hadar T, et al. Cancer of the head and neck region in solid organ transplant recipients. Head Neck 2014; 36:181.
20. Morgan RW, Shelligara PT. Occupational asbestos exposure, smoking and laryngeal carcinoma. Ann NY Sci 1976; 271: 308-310.
21. Guenel P, Chastang J-F, Luce D et al. A study of the interaction of alcohol drinking and tobacco smoking among FRench cases of laryngeal cancer. J Epidermiol omun Health 1988; 42: 350-354.
22. Boffetta P, Hayes RB, Sartori S, et al. Mouthwash use and cancer of the head and neck: a pooled analysis from the International Head and Neck Cancer Epidemiology Consortium. Eur J Cancer Prev 2016; 25:344.
23. Hashim D, Sartori S, Brennan P, et al. The role of oral hygiene in head and neck cancer: results from International Head and Neck Cancer Epidemiology (INHANCE) consortium. Ann Oncol 2016; 27:1619
24. Glanz H, Kleinsasser O. Chronishe laryngitis und carcinom. Arch Ololaryngol 1976; 212: 57-75.
25. Feldman PS, Kaplan MJ, Johns ME et al. Fine-needle aspiration in squamous cell carcinoma of the head and neck. Arch Otolaryngol 1983; 109:735.
26. Pisharodi LR. False-negative diagnosis in fine-needle aspirations of squamous-cell carcinoma of head and neck. Diagn Cytopathol 1997; 17:70.
27. Alkureishi LW, Ross GL, Shoaib T, et al. Sentinel node biopsy in head and neck squamous cell cancer: 5-year follow-up of a European multicenter trial. Ann Surg Oncol 2010; 17:2459.

28. Barzan L, Sulfaro S, Alberti F, et al. An extended use of the sentinel node in head and neck squamous cell carcinoma: results of a prospective study of 100 patients. Acta Otorhinolaryngol Ital 2004; 24:145.
29. Stoeckli SJ, Broglie MA. Sentinel node biopsy for early oral carcinoma. Curr Opin Otolaryngol Head Neck Surg 2012; 20:103.
30. Thompson CF, St John MA, Lawson G, et al. Diagnostic value of sentinel lymph node biopsy in head and neck cancer: a meta-analysis. Eur Arch Otorhinolaryngol 2013; 270:2115.
31. Rodel RM, Steiner W, Muller RM, et al. Endoscopic laser surgery of early glottic cancer: involvement of the anterior commissure. Head Neck 2009; 31:583-592.
32. Zouhair A, Azria D, Coucke P, et al. Decreased local control following radiation therapy alone in early-stage glottic carcinoma with anterior commissure extension. Strahlenther Onkol 2004; 180:84-90.
33. Silver CE, Beitler JJ, Shaha AR, et al. Current trends in initial management of laryngeal cancer: the declining use of open surgery. Eur Arch Otorhinolaryngol 2009; 266:1333-1352.
34. Warner L, Lee K, Homer JJ. Transoral laser microsurgery versus radiotherapy for T2 glottic squamous cell carcinoma: a systematic review of local control outcomes. Clin Otolaryngol 2017; 42:629-636.
35. Yoo J, Lacchetti C, Hammond JA, Gilbert RW. Role of endolaryngeal surgery (with or without laser) versus radiotherapy in the management of early (T1) glottic cancer: a systematic review. Head Neck 2014; 36:1807- 1819.
36. Forastiere AA, Zhang Q, Weber RS, et al. Long-term results of RTOG 91-11: a comparison of three nonsurgical treatment strategies to preserve the larynx in patients with locally advanced larynx cancer. J Clin Oncol 2013; 31:845-852
37. Forastiere AA, Goepfert H, Maor M, et al. Concurrent chemotherapy and radiotherapy for organ preservation in advanced laryngeal cancer. N Engl J Med 2003; 349:2091-2098
38. Janoray G, Pointreau Y, Garaud P, et al. Long-term results of a multicenter randomized phase III trial of induction chemotherapy with cisplatin, 5-fluorouracil, +/- docetaxel for larynx preservation. J Natl Cancer Inst 2016;108
39. Pointreau Y, Garaud P, Chapet S, et al. Randomized trial of induction chemotherapy with cisplatin and 5-fluorouracil with or without docetaxel for larynx preservation. J Natl Cancer Inst 2009; 101:498-506.
40. Semrau S, Schmidt D, Lell M, et al. Results of chemoselection with short induction chemotherapy followed by chemoradiation or surgery in the treatment of functionally inoperable carcinomas of the pharynx and larynx. Oral Oncol 2013; 49:454-460.
41. Lefebvre JL, Pointreau Y, Rolland F, et al. Induction chemotherapy followed by either chemoradiotherapy or bioradiotherapy for larynx preservation: the TREMPLIN randomized

phase II study. J Clin Oncol 2013; 31:853.
42. Stokes WA, Jones BL, Bhatia S, et al. A comparison of overall survival for patients with T4 larynx cancer treated with surgical versus organ-preservation approaches: A National Cancer Data Base analysis. Cancer 2017; 123:600-608.
43. Molin Y, Fayette J. Current chemotherapies for recurrent/metastatic head and neck cancer. Anticancer Drugs 2011; 22:621-625.
44. Hoffmann TK. Systemic therapy strategies for head-neck carcinomas: Current status. GMS Curr Top Otorhinolaryngol Head Neck Surg 2012;11: Doc03.
45. Price KA, Cohen EE. Current treatment options for metastatic head and neck cancer. Curr Treat Options Oncol 2012; 13:35-46.
46. Vermorken JB, Mesia R, Rivera F, et al. Platinum-based chemotherapy plus cetuximab in head and neck cancer. N Engl J Med 2008; 359:1116-1127.
47. Samlowski WE, Moon J, Kuebler JP, et al. Evaluation of the combination of docetaxel/carboplatin in patients with metastatic or recurrent squamous cell carcinoma of the head and neck (SCCHN): a Southwest Oncology Group Phase II study. Cancer Invest 2007; 25:182- 188.
48. Bossi P, Miceli R, Locati LD, et al. A randomized, phase 2 study of cetuximab plus cisplatin with or without paclitaxel for the first-line treatment of patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck. Ann Oncol 2017; 28:2820-2826.
49. Guigay J, Fayette J, Dillies A-F, et al. Cetuximab, docetaxel, and cisplatin (TPEx) as first-line treatment in patients with recurrent or metastatic (R/M) squamous cell carcinoma of the head and neck (SCCHN): Final results of phase II trial GORTEC 2008-03 [abstract]. J Clin Oncol 2012;30(Suppl 15): Abstract 5505.
50. Herbst RS, Arquette M, Shin DM, et al. Phase II multicenter study of the epidermal growth factor receptor antibody cetuximab and cisplatin for recurrent and refractory squamous cell carcinoma of the head and neck. J Clin Oncol 2005; 23:5578-5587.

2.13. Pancreatic Cancer

Epidemiology

Pancreatic cancer is the ranked eighth cancer in both males and Females in the world [1]. It is more frequently seen in men than in women, and more in black than white people [2]. According to 2016 statistical data, it ranks 10th in men in our country. It is not among the top 10 cancers in women. As the age increases towards the 7th decade, it becomes the 6th in both men and women. In our country, it increases every year at a rate of 5.7 per 100000

people per year in men and 3.6 in women [3]. Pancreatic cancer mostly affects western and industrialized countries. It is most common in North America, and western and central Europe [1]. The disease is rare under the age of 45, but increases after the age of 45. It peaks between the ages of 65 and 69 in men and between the ages of 75 and 79 in women [1].

Risk Factors

There are many environmental risk factors in the development of pancreatic cancer. Smoking, diet, alcohol use and high-calorie diet are environmental risk factors. According to the 2017 Global Burden of Disease study data, deaths from pancreatic cancer were found to be associated with smoking, high plasma glucose, and high body mass index [1]. Studies have shown that smoking increases the risk of developing pancreatic cancer by at least 1.5 times [4]. Smoking cessation can reduce the risk of pancreatic cancer by at least 25% [5, 6].

Obesity and physical inactivity increase the risk of pancreatic cancer [7, 8]. According to a study, the risk of developing pancreatic cancer in people with a body mass index of 30 is 1.7 times higher than in people with a body mass index of 23 [9]. In addition, pancreatic cancer occurs at an earlier age in obese and overweight individuals and is associated with shorter life expectancy and lower survival rates [8, 10].

Although the relationship between diet and pancreatic cancer is not yet clear, many studies have shown that high saturated fat intake and western-style meals such as ordinary meat, processed and smoked meat increase the development of pancreatic cancer [11-13]. However, this result was not obtained in all studies [14]. Although some case-control studies have shown that the intake of fresh vegetables and fruits protects against pancreatic cancer, this has not yet been proven in prospective studies [15, 16]. It is stated in the American 2005 Dietary Guidelines that oils found in fruits, vegetables, whole grains, milk, meat, beans, non-hydrogenated plants, and fish reduce the risk of pancreatic cancer. In addition, a diet lower in fat, alcohol and added sugar has been said to have a protective effect. Deficiencies of carotenoids and selenium found in plants have also been found to increase the risk of developing pancreatic cancer, but it is unclear whether this risk can be reduced by diet or supplementation [17, 18].

The information that alcohol and coffee intake increases pancreatic cancer is controversial. Two studies of pooled information have shown an increased risk for heavy drinkers in a small and limited group [19]. The relationship between alcohol use and

pancreatic cancer is often confused with smoking. The relationship between coffee intake and pancreatic cancer is also controversial [20].

Although it is shown in laboratory studies that aspirin and other non-steroidal anti-inflammatory drugs have been shown to suppress pancreatic tumorigenesis, epidemiological data are to the contrary [21, 22]. In a study of approximately 89,000 patients followed for 18 years, regular aspirin use was shown to increase the risk of pancreatic cancer [23]. It has been shown that the risk is increased by 1.8 times in people who take at least 14 tablets of aspirin per week for at least 4 years compared to those who do not use aspirin [23]. However, no increased risk was found in people who took at least 30 tablets of aspirin per month for 20 years [24].

Although weak, a statistically significant relationship was found between Helicobacter pylori and pancreatic cancer. In addition, a correlation was found between hepatitis B and C infection and pancreatic cancer, although not as high as the main cancer of the liver [25].

Numerous studies have found a relationship between diabetes mellitus (DM) and pancreatic cancer [26, 27]. According to the results of a meta-analysis that included 88 studies, it is shown that the risk of developing pancreatic cancer in people with DM is 2 times higher than those without a diagnosis of DM [27]. Etiological factors include abnormal glucose metabolism and insulin resistance [7, 28].

Approximately 5-10% of patients with pancreatic cancer have a family history. While there may be some familial pancreatic cancers, this can also be seen within different genetic predisposition syndromes. For example, while the risk of pancreatic cancer is 2-3 times higher in people with BRCA 1 gene mutations, this risk is between 3.5 and 10 times in BRCA2 carriers [29]. In addition, A, B and 0 blood groups are associated with other gastrointestinal tract tumors, including pancreatic cancer [30]. According to studies, the incidence of pancreatic cancer is higher in non-O groups; which are A, B, and AB blood groups [31]. In addition, patients with cystic fibrosis have a higher risk of pancreatic cancer [32].

Chronic inflammation is a risk factor for pancreatic cancer. Thus, patients with chronic pancreatitis have been shown to have an increased long-term risk of pancreatic cancer, independent of the cause of pancreatitis [33].

Clinical diagnosis and staging

Pancreatic cancer is a highly deadly type of cancer that is the 4th leading cause of death in the United States. Surgery provides definitive treatment, but 15-20% of patients are candidates for pancreatectomy. Even if completely resected, the prognosis is poor. Even in patients with negative surgical margins and no lymph node involvement, the 5-year survival rate is 30% [34].

Ductal adenocarcinoma originating from the ductal epithelium constitutes 85% of pancreatic cancer. Pancreatic gland contains two different cell types, endocrine and exocrine. Cancers consisting of acinar and ductal cells are considered in exocrine pancreatic cancer. Neuroendocrine tumors composed of endocrine cells, on the other hand, constitute 5% of all pancreatic tumors, and their treatment and clinical course are different [35].

Clinical symptoms of pancreatic cancer are usually pain, jaundice, and weight loss. It may also manifest with weakness, loss of appetite, abdominal pain, nausea, vomiting, dark urine, back pain, diarrhea, oily stools, and vascular coagulation and inflammation (thrombophlebitis) [36]. Clinical findings may include jaundice, hepatomegaly, right upper quadrant pain, cachexia, epigastric mass and ascites [36].

Initial clinical reflection depends on tumor localization. Exocrine pancreatic cancers occur most frequently in the head of the pancreas, then in the body part and less frequently in the tail [37]. Tumors developing in the head of the pancreas usually reflect themselves in clinics with jaundice, fatty stools, and weight loss [38].

Pain is one of the most common symptoms and can occur even when the mass is 2 cm [39]. The pain usually starts from the epigastric region and spreads from both sides to the back. It increases with food, is intermittent and passes when leaning forward. It usually increases at night. Sometimes, as a result of occlusion of the pancreatic duct due to the mass, acute pancreatitis attacks and pain can quickly reflect the clinic [40].

Jaundice is an early finding that occurs as a result of the mass in the head of the pancreas obstructing the pancreatic biliary tract and is progressive. Sometimes, there may be jaundice due to liver metastases [41]. In people diagnosed with pancreatic cancer, DM can be diagnosed simultaneously or 1-2 years earlier. Although the age of onset of pancreatic cancer and DM are similar, DM may start 1-2 years before pancreatic cancer in 25% of

patients. Therefore, a study on screening patients with new-onset DM for pancreatic cancer was conducted, but it was inconclusive [42, 43].

Unexplained superficial and sometimes migratory thrombophlebitis shows the effect of pancreatic cancer on the coagulation system. It is a sign of advanced disease and is observed in both arteries and veins. Multiple arterial thrombophlebitis can cause endocarditis of the heart. Thrombophlebitis is usually seen in disease of the tail and body [44].

There may be clinical reflections with metastatic disease. The liver, peritoneum and lungs are often affected and less often bone is affected. Depending on these, a mass and ascites in the abdomen, enlargement of the left supraclavicular lymph node, and a palpable mass around the umbilicus may be present on physical examination. Sometimes it can be detected incidentally on a tomography taken for another reason [45].

When a pancreatic mass is detected, cystic solid should be differentiated first, and if it is a solid mass, a differential diagnosis of exocrine pancreatic cancer, endocrine pancreatic cancer, lymphoma, metastatic cancer, focal pancreatitis, and autoimmune pancreatitis should be made.

In diagnostic tests, laboratory values are first applied. After checking aminotransferase and alkaline phosphatase and bilirubin in serum, lipase for pancreatic resection and carbohydrate antigen 19-9 (CA19-9) as a cancer marker can be checked. In a patient with jaundice, ultrasound imaging (USG) is appropriate primarily because of its high sensitivity [46]. For patients with suspected choledochal duct stones, endoscopic retrograde choledocopancreatography (ERCP) and magnetic resonancescolangiopancreatography (MRCP) may be considered. Computed tomography (CT) evaluation is recommended in patients without jaundice, presenting with epigastric pain and weight loss [47].

After the mass is seen on radiological imaging, if the mass is not suspicious and thought to be a resectable disease, there is no need for a biopsy beforehand. However, if the mass is suspicious and its resectability is uncertain, additional procedures are needed. In some cases, magnetic resonance (MR) may be more appropriate to assess for spread and metastasis. Evaluation with ERCP may be required not only for stones in the common bile duct, but also for cases with a mass in the head of the pancreas [48]. Bilirubin drainage is provided by stenting. In patients who cannot tolerate ERCP, MRCP may be an option, but

treatment cannot be applied [49]. Endoscopic USG is sometimes used for diagnosis and mostly for staging [50].

As a tumor marker, the sensitivity of CA19-9 ranges from 70–92%, and its specificity ranges from 68–92% [51, 52]. Its sensitivity is related to tumor size. Its sensitivity is on limit in small tumors [51]. According to blood group type, CA19-9 is not an auxiliary marker in 5-10% of Lewis antigen-negative patients [53]. It can be elevated not only in pancreatic cancer, but also in benign pancreaticobiliary diseases. Although a study showed that a cut-off value of 37 units/ml can be used to differentiate between cancer and benign lesions, CA19-9 is not used in screening [54]. It can be tested in patients with clinical symptoms and a pancreatic mass. Although there is no clear cut-off value, CA19-9 is usually high in cancer patients, but it has been shown to increase up to 10,000 units/ml even in benign lesions. [55]. The rate of elevation of the CA19-9 marker provides information about the long-term disease course. Elevations at the beginning of the disease and after the operation indicate the disease prognosis. In addition, the rate of elevation in diagnosis may be a guide for surgical staging and treatment [56, 57].

Percutaneous biopsy and endoscopic USG-guided biopsy can be performed for diagnosis. The percutaneous biopsy can be performed under USG or CT guidance. The choice can be made according to the size of the tumor and the experience of the person performing the biopsy. Theoretically, it can be considered that a percutaneous biopsy performed may be tumor seeding with tumor cells spilled into the peritoneum, but such a risk is negligible [58]. Endoscopic USG-guided biopsy is suitable for tumors that cannot be assessed well on imaging. Peritoneal tumor transplantation is less likely and carries a risk of intestinal perforation. Its sensitivity (90%) and specificity (96%) are high [59].

In staging, all exocrine and endocrine pancreatic cancers are staged according to the 8th edition (2017) of the Tumor Node Metastasis (TNM) System with the combination of the American Joint Cancer Committee-AJCC and Union for International Cancer Control-UICC [34]. Staging is necessary to understand the extent of the disease and to decide which patient should be resected. Thin section helical CT with three-phase contrast multidetector is recommended for staging. It is suitable for visualizing the main pancreatic duct and small tumors [60]. Venous and arterial phases can be visualized. In this way, the superior mesenteric vein and artery and the celiac axis are visualized, which are important for the

resection decision [61]. In addition, its sensitivity is high in detecting liver metastases, but it cannot show sufficient success in peritoneal and lymph node involvement [62, 63]. The usefulness of positron emulsion tomography (PET) in the diagnosis and staging of pancreatic cancer is questionable. Its sensitivity ranges between 73-94% and specificity ranges between 60-89% at initial use. It is useful in detecting low-volume metastases missed by helical tomography [64, 65]. It may be false-negative in hyperglycemic patients, as well as false-positive in cases of stent-related local inflammation, infected pseudocyst, and pancreatitis [65].

In patients with pancreatic cancer, laparoscopic surgical staging is performed to avoid unnecessary laparotomy, mostly due to the presence of unresectable patients at diagnosis. Laparoscopic staging is recommended in patients with advanced vascular involvement but not completely occluded, in patients with a mass in the body and tail of the pancreas but without jaundice, who are scheduled for laparotomy but with CA19-9 > 1000 units/ml and for whom neoadjuvant therapy will be initiated [66]. Peritoneal cytology is a procedure performed during laparoscopy and affects the resection decision. Since it is positive, it indicates the presence of metastases in the liver, omentum, or pelvis and is considered metastatic according to TNM staging [67].

Finally, in people diagnosed with pancreatic cancer, the American Society of Clinical Oncology-ASCO recommends evaluating individual and familial factors with good family history and looking for germline mutations in cases with familial pancreatic cancer [68].

Treatment

Surgical resection is the only curative treatment method, but only 15-20% of patients are candidates for pancreatectomy due to the late presentation of the disease [34]. There are patients who can be resected at the border. Technically, it is necessary to consider the long-term prognosis, even if there are patients who can be operated on. Neoadjuvant chemotherapy may be considered in patients with marginally resectable or unresectable locally advanced disease but without distant metastases [69]. The surgical method varies according to the location of the tumor in the pancreas and vascular involvement. The stage is the most important prognostic factor in pancreatic cancer. Additional factors are surgical margin status, tumor differentiation, lymphatic invasion, CA19-9 level before and after surgery and smoking history [70–72]. Lymph node involvement also has prognostic

significance [34].

In metastatic disease, platinum-based combination chemotherapy and maintenance treatment with some targeted drugs in patients with genetic mutations are planned to prolong survival. Treatment should be planned for each patient by evaluating his/her own clinical and pathological characteristics.

RESOURCES

1. Collaborators GBDPC. The global, regional, and national burden of pancreatic cancer and its attributable risk factors in 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet Gastroenterol Hepatol 2019; 4(issue): 934-947.
2. Ministry of Health Ankara Local Health Authority, Turkey Cancer Statistics 2016, Ankara 2019.
3. Howlader N, Noone AM, Krapcho M et all. SEER Cancer Statistics Review, 1975-2016, National Cancer Institute. Bethesda, MD, https://seer.cancer.gov/csr/1975_2016/, based on November 2018 SEER data submission, posted to the SEER web site, April 2019. https://seer.cancer.gov/csr/1975_2017/ (Accessed on May 01, 2020).
4. Lynch SM, Vrieling A, Lubin JH, et al. Cigarette smoking and pancreatic cancer: a pooled analysis from the pancreatic cancer cohort consortium. Am J Epidemiol 2009; 170(issue): 403-413.
5. Silverman DT, Dunn JA, Hoover RN, et al. Cigarette smoking and pancreas cancer: a case-control study based on direct interviews. J Natl Cancer Inst 1994; 86(issue): 1510-1516.
6. Fuchs CS, Colditz GA, Stampfer MJ, et al. A prospective study of cigarette smoking and the risk of pancreatic cancer. Arch Intern Med 1996; 156(issue): 2255-2260.
7. Carreras-Torres R, Johansson M, Gaborieau V, et al. The Role of Obesity, Type 2 Diabetes, and Metabolic Factors in Pancreatic Cancer: A Mendelian Randomization Study. J Natl Cancer Inst 2017; 109(issue).
8. Li D, Morris JS, Liu J, et al. Body mass index and risk, age of onset, and survival in patients with pancreatic cancer. JAMA 2009; 301(issue): 2553-2562.
9. Michaud DS, Giovannucci E, Willett WC, et al. Physical activity, obesity, height, and the risk of pancreatic cancer. JAMA 2001; 286(issue): 921-929.
10. Yuan C, Bao Y, Wu C, et al. Prediagnostic body mass index and pancreatic cancer survival. J Clin Oncol 2013; 31(issue): 4229-4234.
11. Nothlings U, Wilkens LR, Murphy SP, et al. Meat and fat intake as risk factors for pancreatic

cancer: the multiethnic cohort study. J Natl Cancer Inst 2005; 97(issue): 1458-1465.

12. Silverman DT, Swanson CA, Gridley G, et al. Dietary and nutritional factors and pancreatic cancer: a case-control study based on direct interviews. J Natl Cancer Inst 1998; 90(issue): 1710-1719.
13. Larsson SC, Wolk A. Red and processed meat consumption and risk of pancreatic cancer: meta-analysis of prospective studies. Br J Cancer 2012; 106(issue): 603-607.
14. Michaud DS, Giovannucci E, Willett WC, et al. Dietary meat, dairy products, fat, and cholesterol and pancreatic cancer risk in a prospective study. Am J Epidemiol 2003; 157(issue): 1115-1125.
15. Howe GR, Jain M, Miller AB. Dietary factors and risk of pancreatic cancer: results of a Canadian population-based case-control study. Int J Cancer 1990; 45(issue): 604-608.
16. Coughlin SS, Calle EE, Patel AV, et al. Predictors of pancreatic cancer mortality among a large cohort of United States adults. Cancer Causes Control 2000; 11(issue): 915-923.
17. Burney PG, Comstock GW, Morris JS. Serologic precursors of cancer: serum micronutrients and the subsequent risk of pancreatic cancer. Am J Clin Nutr 1989; 49(issue): 895-900.
18. Han X, Li J, Brasky TM, et al. Antioxidant intake and pancreatic cancer risk: the Vitamins and Lifestyle (VITAL) Study. Cancer 2013; 119(issue): 1314-1320.
19. Michaud DS, Vrieling A, Jiao L, et al. Alcohol intake and pancreatic cancer: a pooled analysis from the pancreatic cancer cohort consortium (PanScan). Cancer Causes Control 2010; 21(issue): 1213-1225.
20. Turati F, Galeone C, Edefonti V, et al. A meta-analysis of coffee consumption and pancreatic cancer. Ann Oncol 2012; 23(issue): 311-318.
21. Schreinemachers DM, Everson RB. Aspirin use and lung, colon, and breast cancer incidence in a prospective study. Epidemiology 1994; 5(issue): 138-146.
22. Anderson KE, Johnson TW, Lazovich D, et al. Association between nonsteroidal anti-inflammatory drug use and the incidence of pancreatic cancer. J Natl Cancer Inst 2002; 94(issue): 1168-1171.
23. Schernhammer ES, Kang JH, Chan AT, et al. A prospective study of aspirin use and the risk of pancreatic cancer in women. J Natl Cancer Inst 2004; 96(issue): 22-28.
24. Jacobs EJ, Connell CJ, Rodriguez C, et al. Aspirin use and pancreatic cancer mortality in a large United States cohort. J Natl Cancer Inst 2004; 96(issue): 524-528.
25. Huang J, Magnusson M, Torner A, et al. Risk of pancreatic cancer among individuals with hepatitis C or hepatitis B virus infection: a nationwide study in Sweden. Br J Cancer 2013; 109(issue): 2917-2923.
26. Calle EE, Murphy TK, Rodriguez C, et al. Diabetes mellitus and pancreatic cancer mortality in a prospective cohort of United States adults. Cancer Causes Control 1998; 9(issue): 403-

410.

27. Batabyal P, Vander Hoorn S, Christophi C, et al. Association of diabetes mellitus and pancreatic adenocarcinoma: a meta-analysis of 88 studies. Ann Surg Oncol 2014; 21(issue): 2453-2462.
28. Stolzenberg-Solomon RZ, Graubard BI, Chari S, et al. Insulin, glucose, insulin resistance, and pancreatic cancer in male smokers. JAMA 2005; 294(issue): 2872-2878.
29. Klein AP, Hruban RH, Brune KA, et al. Familial pancreatic cancer. Cancer J 2001; 7(issue): 266-273.
30. Risch HA, Yu H, Lu L, et al. ABO blood group, Helicobacter pylori seropositivity, and risk of pancreatic cancer: a case-control study. J Natl Cancer Inst 2010; 102(issue): 502-505.
31. Wolpin BM, Chan AT, Hartge P, et al. ABO blood group and the risk of pancreatic cancer. J Natl Cancer Inst 2009; 101(issue): 424-431.
32. Yamada A, Komaki Y, Komaki F, et al. Risk of gastrointestinal cancers in patients with cystic fibrosis: a systematic review and meta-analysis. Lancet Oncol 2018; 19(issue): 758-767.
33. Lowenfels AB, Maisonneuve P, Cavallini G, et al. Pancreatitis and the risk of pancreatic cancer. International Pancreatitis Study Group. N Engl J Med 1993; 328(issue): 1433-1437.
34. Allen PJ, Kuk D, Castillo CF, et al. Multi-institutional Validation Study of the American Joint Commission on Cancer (8th Edition) Changes for T and N Staging in Patients With Pancreatic Adenocarcinoma. Ann Surg 2017; 265(issue): 185-191.
35. Klimstra DS. Nonductal neoplasms of the pancreas. Mod Pathol 2007; 20 Suppl 1(issue): S94-112.
36. Porta M, Fabregat X, Malats N, et al. Exocrine pancreatic cancer: symptoms at presentation and their relation to tumour site and stage. Clin Transl Oncol 2005; 7(issue): 189-197.
37. Modolell I, Guarner L, Malagelada JR. Vagaries of clinical presentation of pancreatic and biliary tract cancer. Ann Oncol 1999; 10 Suppl 4(issue): 82-84.
38. Bakkevold KE, Arnesjo B, Kambestad B. Carcinoma of the pancreas and papilla of Vater: presenting symptoms, signs, and diagnosis related to stage and tumour site. A prospective multicentre trial in 472 patients. Norwegian Pancreatic Cancer Trial. Scand J Gastroenterol 1992; 27(issue): 317-325.
39. Furukawa H, Okada S, Saisho H, et al. Clinicopathologic features of small pancreatic adenocarcinoma. A collective study. Cancer 1996; 78(issue): 986-990.
40. Mujica VR, Barkin JS, Go VL. Acute pancreatitis secondary to pancreatic carcinoma. Study Group Participants. Pancreas 2000; 21(issue): 329-332.
41. Kalser MH, Barkin J, MacIntyre JM. Pancreatic cancer. Assessment of prognosis by clinical presentation. Cancer 1985; 56(issue): 397-402.

42. Chari ST, Leibson CL, Rabe KG, et al. Probability of pancreatic cancer following diabetes: a population-based study. Gastroenterology 2005; 129(issue): 504-511.
43. Aggarwal G, Kamada P, Chari ST. Prevalence of diabetes mellitus in pancreatic cancer compared to common cancers. Pancreas 2013; 42(issue): 198-201.
44. Khorana AA, Fine RL. Pancreatic cancer and thromboembolic disease. Lancet Oncol 2004; 5(issue): 655-663.
45. Goodman M, Willmann JK, Jeffrey RB. Incidentally discovered solid pancreatic masses: imaging and clinical observations. Abdom Imaging 2012; 37(issue): 91-97.
46. Karlson BM, Ekbom A, Lindgren PG, et al. Abdominal US for diagnosis of pancreatic tumor: prospective cohort analysis. Radiology 1999; 213(issue): 107-111.
47. Brand R. The diagnosis of pancreatic cancer. Cancer J 2001; 7(issue): 287-297.
48. Niederau C, Grendell JH. Diagnosis of pancreatic carcinoma. Imaging techniques and tumor markers. Pancreas 1992; 7(issue): 66-86.
49. Varghese JC, Farrell MA, Courtney G, et al. Role of MR cholangiopancreatography in patients with failed or inadequate ERCP. AJR Am J Roentgenol 1999; 173(issue): 1527-1533.
50. Wang W, Shpaner A, Krishna SG, et al. Use of EUS-FNA in diagnosing pancreatic neoplasm without a definitive mass on CT. Gastrointest Endosc 2013; 78(issue): 73-80.
51. Pleskow DK, Berger HJ, Gyves J, et al. Evaluation of a serologic marker, CA19-9, in the diagnosis of pancreatic cancer. Ann Intern Med 1989; 110(issue): 704-709.
52. Cwik G, Wallner G, Skoczylas T, et al. Cancer antigens 19-9 and 125 in the differential diagnosis of pancreatic mass lesions. Arch Surg 2006; 141(issue): 968-973; discussion 974.
53. Tempero MA, Uchida E, Takasaki H, et al. Relationship of carbohydrate antigen 19-9 and Lewis antigens in pancreatic cancer. Cancer Res 1987; 47(issue): 5501-5503.
54. Kim JE, Lee KT, Lee JK, et al. Clinical usefulness of carbohydrate antigen 19-9 as a screening test for pancreatic cancer in an asymptomatic population. J Gastroenterol Hepatol 2004; 19(issue): 182-186.
55. Kim HJ, Kim MH, Myung SJ, et al. A new strategy for the application of CA19-9 in the differentiation of pancreaticobiliary cancer: analysis using a receiver operating characteristic curve. Am J Gastroenterol 1999; 94(issue): 1941-1946.
56. Karachristos A, Scarmeas N, Hoffman JP. CA 19-9 levels predict results of staging laparoscopy in pancreatic cancer. J Gastrointest Surg 2005; 9(issue): 1286-1292.
57. Khorana AA, Mangu PB, Berlin J, et al. Potentially Curable Pancreatic Cancer: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol 2016; 34(issue): 2541-2556.
58. Johnson DE, Pendurthi TK, Balshem AM, et al. Implications of fine-needle aspiration in

patients with resectable pancreatic cancer. Am Surg 1997; 63(issue): 675-679; discussion 679-680.

59. Chang KJ, Nguyen P, Erickson RA, et al. The clinical utility of endoscopic ultrasound-guided fine-needle aspiration in the diagnosis and staging of pancreatic carcinoma. Gastrointest Endosc 1997; 45(issue): 387-393.
60. Smith SL, Rajan PS. Imaging of pancreatic adenocarcinoma with emphasis on multidetector CT. Clin Radiol 2004; 59 (issue): 26-38.
61. Wong JC, Raman S. Surgical resectability of pancreatic adenocarcinoma: CTA. Abdom Imaging 2010; 35(issue): 471-480.
62. Motosugi U, Ichikawa T, Morisaka H, et al. Detection of pancreatic carcinoma and liver metastases with gadoxetic acid-enhanced MR imaging: comparison with contrast-enhanced multi-detector row CT. Radiology 2011; 260(issue): 446-453.
63. Reddy KR, Levi J, Livingstone A, et al. Experience with staging laparoscopy in pancreatic malignancy. Gastrointest Endosc 1999; 49(issue): 498-503.
64. Farma JM, Santillan AA, Melis M, et al. PET/CT fusion scan enhances CT staging in patients with pancreatic neoplasms. Ann Surg Oncol 2008; 15(issue): 2465-2471.
65. Rijkers AP, Valkema R, Duivenvoorden HJ, et al. Usefulness of F-18-fluorodeoxyglucose positron emission tomography to confirm suspected pancreatic cancer: a meta-analysis. Eur J Surg Oncol 2014; 40(issue): 794-804.
66. Fong ZV, Alvino DML, Fernandez-Del Castillo C, et al. Reappraisal of Staging Laparoscopy for Patients with Pancreatic Adenocarcinoma: A Contemporary Analysis of 1001 Patients. Ann Surg Oncol 2017; 24(issue): 3203-3211.
67. Warshaw AL. Implications of peritoneal cytology for staging of early pancreatic cancer. Am J Surg 1991; 161(issue): 26-29; discussion 29-30.
68. Stoffel EM, McKernin SE, Brand R, et al. Evaluating Susceptibility to Pancreatic Cancer: ASCO Provisional Clinical Opinion. J Clin Oncol 2019; 37(issue): 153-164.
69. Hackert T, Sachsenmaier M, Hinz U, et al. Locally Advanced Pancreatic Cancer: Neoadjuvant Therapy with Folfirinox Results in Resectability in 60% of the Patients. Ann Surg 2016; 264(issue): 457-463.
70. Geer RJ, Brennan MF. Prognostic indicators for survival after resection of pancreatic adenocarcinoma. Am J Surg 1993; 165(issue): 68-72; discussion 72-63.
71. Kinsella TJ, Seo Y, Willis J, et al. The impact of resection margin status and postoperative CA19-9 levels on survival and patterns of recurrence after postoperative high-dose radiotherapy with 5-FU-based concurrent chemotherapy for resectable pancreatic cancer. Am J Clin Oncol 2008; 31(issue): 446-453.
72. Yuan C, Morales-Oyarvide V, Babic A, et al. Cigarette Smoking and Pancreatic Cancer

Survival. J Clin Oncol 2017; 35(issue): 1822-1828.

2.14. Brain and Nervous System Cancers

Cancer is defined as the uncontrolled proliferation of cells and is one of the most important health problems involving various organs or systems of the body. The response of the organs or systems to the disease, the clinical course and treatments of cancers also differ.

The cancer-affected area of the nervous system differs from other cancers of the body by directly or indirectly affecting other systems. These cancers either originate directly from the brain (primary) or originate from other organs and spread to the brain (metastasize). In general, the clinical picture of all brain cancers is closely similar.

Their general incidence varies between 3-7 per hundred thousand. Although there are positive developments in the life expectancy and quality of these patients thanks to the the combined treatments (surgery, radiotherapy, chemotherapy, gamma knife, gene therapies), the vast majority of them are lost in 6-18 months on average by repetition or spread. Although new biochemical and genetic studies in recent years are promising, any clinical study that resulted in cure is not reported yet.

In this article, general current information about brain cancers in our country and in the world has been compiled by using various sources [1-8].

Statistics in Our Country and In the World: In general, the term nervous system cancers includes brain, spinal cord cancers, and peripheral nerve cancers, although in lower numbers. Since these tumors constitute the primary group (glioblastoma multiforma, anaplastic astrocytoma, medulloblastoma, etc.) and metastases, these tumors will be covered more in the article.

As in the world, the number of patients with brain cancer in our country varies according to years and geographical regions. While brain cancers are in the 10th rank among adult cancers seen in our country, childhood brain tumors constitute the second most common group of tumors, after leukemia.

Gliomas are the most common primary cancers in adults and the most common of them is glioblastoma multiforme. Their rate among all brain tumors in our country is 22.4%, and they are more common in men than in women (M/F: 7/5 per hundred thousand). The incidence of these tumors in other countries varies between 3-6 per hundred thousand. The

situation is different in children, with medulloblastomas being the most commonly seen and accounting for 20 percent of all primary pediatric brain/cerebellum/brainstem tumors.

Metastases, on the other hand, constitute the second most common group after gliomas among all brain tumors in adults, and in some series, they are the adult brain cancers that take the first place clinically. They frequently spread to the brain from organs such as lungs and breast, intestine, prostate and skin.

In our country, brain cancer and other cancers of the nervous system (in the records of the Ministry of Health of the Republic of Turkey, it is referred as originating from the brain and meninges) have increased in all cancer mortality rates in recent years, according to the data of the General Directorate of Public Health of the Ministry of Health. While its incidence was 0.9% in death rates in 2012, this rate was reported as 7% in 2016.

In childhood, nervous system tumors (mostly medulloblastoma, ependymoma, astrocytoma) are the second most common tumors after leukemia, consisting 30% of all tumors.

In studies conducted in different countries, the incidence of brain cancers (glial tumors, metastatic tumors) in general has been reported to be between 3-7 per hundred thousand, also depending on the localities.

The most comprehensive clinical study in our country in terms of the distribution of cases diagnosed with brain cancer by regions is the Turkish Neurosurgery Society Neurooncology Group (TURNOG) study. In this study, the number of cases diagnosed with brain tumors, especially high-grade glioma, was grouped by region. For example, while the rate of high-grade gliomas among other brain tumors was determined as 57% in Trabzon, this rate was determined as 7% in Hatay.

Especially the registry system related to brain cancers is very important in determining the incidence. Technological development in diagnosis and increase in diseases are the most effective factors determining the current rate. In this regard, it may be possible to reveal concrete results for the upcoming period by compiling solid data, together with the studies of the relevant cancer institutions within the Ministry of Health [1,3-5, 7-15, 17].

Risk Factors: It is stated that ionizing radiation, familial (genetic) predisposition, previous

radiotherapy and chemotherapy play a role among the possible risk factors in the development of brain cancers. In addition, there are some studies supporting that it is more common in people with allergies (asthma, eczema-like diseases), and that the magnetic waves emitted by mobile phones and similar devices may also play a role. The most important factors are smoking in metastatic lung cancers, diet in colon cancers, and the risk of excessive sun exposure in skin cancers. Brain metastases have been reported to occur in approximately 15-30% of all cancer patients [4,5,16,17,18]**.**

Signs and Symptoms in Brain Cancers: Signs and symptoms vary according to the type, size, location and growth rate of the tumor. Headache, nausea and vomiting (especially in the morning), usually due to the increase in intracranial pressure by the tumor in the brain, are the most common complaints. In addition, there may also be complaints and symptoms such as seizures (epileptic seizures), eye problems (blurred vision, double vision, narrowing of the visual field), weakness, and sensory disorders in half of the body (arm and leg) or the whole body, problems with memory, perception, thinking and concentration, balance disorders, behavioral or personality changes, hearing problems, urination or defecation problems, accompanying or independent of these complaints. However, it should be kept in mind that some of these complaints may also be related to some other diseases.

Especially in childhood brain tumors, the findings may differ from adults. Complaints and findings may be overlooked due to the inability of children to express themselves adequately. For this reason, especially childhood headaches should be taken seriously. If there are symptoms due to compression on the brain, the course of life quality and duration can be changed positively without causing loss of function, by making the necessary appropriate intervention.

Sometimes, brain tumors may not show any symptoms, and sometimes they may be detected incidentally while investigating the causes of some atypical complaints, such as general body weakness, or during imaging examinations taken for examination purposes.

The course and severity of metastatic brain tumors generally affect the brain in parallel with the severity in the primary organ. Sometimes, they can be seen only in the brain with the first symptoms as a result of direct spread, without symptoms in the primary organ [1,3,10-12,16,19].

Prevention, Protection and Treatment of Brain and Nerve Cancers: Early diagnosis is important for prevention. Radioactive substances are defined to play the most important role so far, among the causes. The presence of neurofibromatosis type I, optic glioma partially supports the role of genetic factors.

Various protocols have been developed on follow-up status after diagnosis, surgery and post-operative treatments, and some protocols have been standardized within the framework of multidisciplinary teamwork (neurosurgery, medical oncology and radiation oncology specialists), although they sometimes vary according to medical innovations.

There are many methods for the treatment of brain tumors. In addition to surgical treatment, methods such as general radiation therapy (radiation), local radiosurgery (radial therapy), medical therapy (chemotherapy) are also applied separately or in combination. Immunotherapy treatment has also started to be applied and it is promising for the future [2,4,6,9, 16-20].

Diagnosis in Brain and Nerve Cancers: Laboratory, Imaging, Biopsy: Depending on the situation whether it develops as a result of the spread of a tumor in its own tissue or elsewhere in the body to the brain via blood, the diagnostic approach may also be different. The first group includes high-grade tumors that develop from the brain's own tissue. Computed brain tomography (CBT) and magnetic resonance imaging (MRI) are the most commonly used imaging methods for diagnosis **(Figure 5: Example case, MRI image of glioblastoma multiforme, one of the primary brain tumors)**, and in the second group, metastases that develop elsewhere in the body and spread to the brain via blood **(Figure: 6: Example case, MRI image of cancer metastasis of lung cancer to the brain)**.

Although CT and MRI are the most frequently used diagnostic methods in the diagnosis, imaging examinations such as direct radiography, ultrasonography, positron emission tomography (PET), single positron emission tomography (SPECT) and whole-body bone scintigraphy are also frequently used examinations, aiming to determine the focus of the tumor, the organs and regions where the tumor originates, especially in metastatic brain tumors. Although advanced imaging studies support the diagnosis to a great extent, histopathological examination is still considered the most definitive diagnostic method today.

In the histological diagnosis, the result determined in the examination of the tumor tissue taken by stereotaxic biopsy, burr hole (taking a piece from the hole made in the head) or craniotomy (removing a part of the skull bone and replacing it) is used as the basis of the treatment, and these results have a direct impact on the quality and duration of life. In the diagnosis of metastases, researches for primary organ examination form the basis of diagnosis and treatment in the first place [12,16, 18, 19].

Staging in Brain and Nerve Cancers: Glial tumors are graded as low grade (grade I, II) and high grade (grade III, IV) glial tumors and grade IV is considered the heaviest.

Low-grade tumors generally grow more slowly than high-grade tumors, and although their margins to the brain are not very clear, recurrence or spread to other parts of the body is also possible even after they are almost entirely removed, but their growth and recurrence are generally slower than high-grade tumors. The need for chemotherapy or radiotherapy after surgery is lower. Sometimes, however, there may be differences in approach due to algorithms and individual comorbid disease or other medical reasons. Sometimes, the treatment planned for each patient may differ and take the form of a personalized treatment.

Metastatic brain tumors are generally accepted as advanced stage tumors. As a result of the spread of malignant tumor cells to the brain, it settles there by making single or multiple transplantations. They develop as a result of organ cancers such as lung, breast, skin, large intestines, prostate and skin spreading to the brain via blood. They grow faster than benign tumors. Its borders and color difference with the brain may not always differ significantly. It may not be possible to completely remove them with surgery, and even if they are removed almost completely, the probability of recurrence is high. They can recur in the same part of the brain, or they can spread to other parts of the brain, spinal cord or other parts of the body.

Radiotherapy and chemotherapy are usually/absolutely necessary in order to prevent their reoccurrence, albeit partially, or to stop or destroy the existing one. In recent years, some clinical studies on immunotherapy applications also continue to be promising for the future [4,6,9,17,19,23,24].

Treatment of Brain and Nerve Cancers: Surgery, Oncological Treatment, Follow-up:

Appropriate treatment for each patient should be planned with a multidisciplinary

approach, taking into account the functional and cognitive status and comorbid diseases. For appropriate treatment, first of all, it is necessary to make a definitive diagnosis, and for this, it is aimed to remove the tumor part of the brain tumor that can be removed without causing additional problems to the patient as much as possible. Generally, if there is pressure on the brain and the patient is suitable for surgery, surgery is prioritized in order to reduce or eliminate the pressure, as well as to establish a definitive diagnosis. After surgery, intermediate and high grade glial tumors and metastases are also followed up and treated by the oncology department. In recent years, as a result of molecular and genetic studies, it has been determined that glioblastoma multiforma (glial tumor grade IV) has subtyping within itself and that molecular diagnostic markers of them have serious effects on survival. Their mortality and morbidity are high. In general, the average life expectancy is 1-1.5 years, even when surgical and oncological treatment are applied together. There may be cases that live longer, but the average survival rate for 5 years is 3-5% in these cases. Patients are usually followed up in 1, 3 and 6 months' periods, but if the survival is long, longer follow-up may be appropriate for some cases.

If the patient's condition is severe, the lesion is small, deep, or spreads rapidly, it is very important to make a diagnosis rather than removing the lesion completely. If the patient is not able to bear the surgery, the diagnosis should be made only by biopsy, if necessary. This can be done by biopsy, either by a small craniotomy or by making a hole in the head. Owing to the developing technology, even small lesions can be easily biopsied with stereotactic surgery or neuronavigation, if necessary, and with fewer complications.

Response to treatment also depends on factors such as the size of the tumor, the focus/organ from which it originated, the extent of spread (the area of spread, the number of organs), the number of lesions, the age of the patient and the status of other comorbid diseases [5,6,9,18-20].

Prognosis in Brain and Nerve Cancers: The natural course of brain cancers is generally poor. However, prolonging the survival time of these cases is the primary goal. Success in this goal depends on the type, size, grade of the tumor, and region of involvement. In general, survival is about 1 year in primary tumors, but young age, the good neurologic status of the patient, removal of it as unproblematic as possible with the surgery performed, and favorable advanced histopathological and genetic indicators affect the survival time positively.

In metastases, the patient may die within months without treatment, and the duration may increase significantly with combined treatments. Gamma knife, chemotherapy and radiotherapy, applied before or after the surgery according to the indication, positively affect the survival for a few (3-5) months. In primary brain cancers, the average survival rate is 1 year. The two-year survival rate is 30%, and the three-year and above survival rate is between 1-5% [3, 4, 8, 9, 21].

Conclusion: Currently a permanent solution has not been developed for brain cancers yet. Despite combined treatments, their course still results in severe conclusions. Ongoing clinical and experimental studies (immunological, biochemical and genetic) keep our hopes alive for the future.

Making the current patient registration systems meticulously and making them more regular will not only determine the objective situation, but also make serious contributions to future planning.

Recording changes according to age, gender, and geographical characteristics in our country are very important in determining future scientific studies and strategies (diagnosis, treatments, and follow-up) on brain cancers.

In this regard, the activities of brain and neurosurgery and other cancer-related branches in the cancer research, registry and monitoring centers in our country, including regularly recording these cases, supporting them with their data, and cooperating with these centers will make significant contributions to future planning [3, 4, 9, 17, 25].

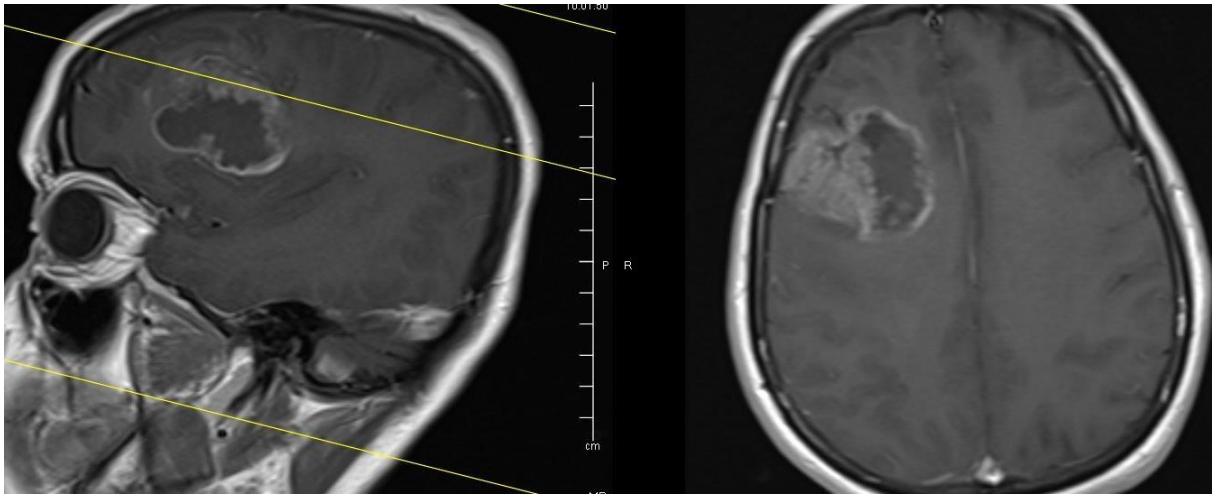


Figure 5. Primary Brain Cancer, (Glioblastoma Multiforme)

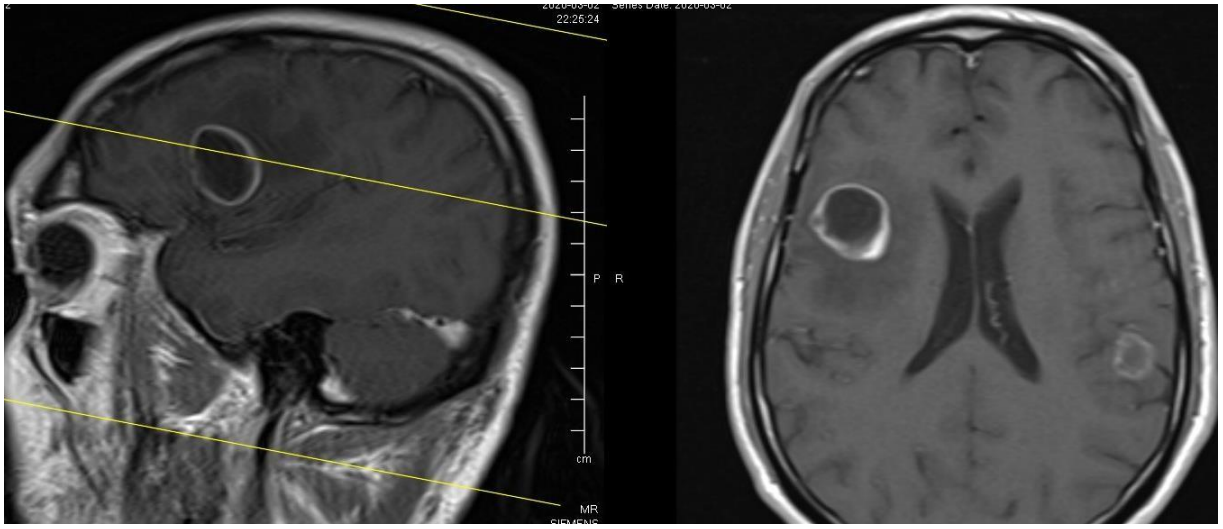


Figure 6. Metastatic (Lung-derived) Brain Cancer

RESOURCES

1. Greenberg MS. Cerebral Metastases. Handbook of Neurosurgery, Fifth edition, New York, Thiema p.2001, 463-469.
2. Silantyev AS, Falzone L, Libra M, et al. Current and Future Trends on Diagnosis and Prognosis of Glioblastoma: From Molecular Biology to Proteomics. Cells. 2019; 9;8(8).
3. Turkey Cancer Control Programme (ISBN): 978-975-590-593-8, TR. Editors: Keskinkılıç B, Gültekin M, Koca AS et al. Ministry of Health Publication No: 978,1. Edition, Ankara, 2016. https://docplayer.biz.tr/9581327-Turkiye-kanser-kontrol-programi.html (03.08.2020).
4. Oktar N, Akakın A, Hakan T, et al. TURNOG High Stage Gliomas Workshop 2nd group. TURNOG symposium, Istanbul, 1-2. 12. 2006.
5. Low Grade Glial Tumors and Treatment Algorithm. Journal of TURNOG (Turkish Neurosurgical Society Neurooncological Surgery Education and Training Group) issue 7 p.10. 2009. http://www.turnog.com/turnogDATA/Books/2/bulten-7.pdf (03.08.2020).
6. Bekar A, Ceçener G, Tunca B, et al. Investigation of mutations and expression of the FHIT gene in Turkish patients with metastases brain derived from non-small cell lung cancer Tumori. 2007; 93: 604-607.
7. Erdis E, Yucel B, Urvay S, et al. Overview of Survivaland Related Parameters in Malignancies with Brain Metastasis, Turk J Oncol 2016;31(3):97-103
8. Dobes M, Khurana VG, Shadbolt B, et al. Increasing incidence of glioblastoma multiforme and meningioma, and decreasing incidence of Schwannoma (2000-2008): Findings of a multicenter Australian study.Surg Neurol Int. 2011; 2:176.

9. 9.https://www.nhsinform.scot/illnesses-and-conditions/cancer/cancer-types-in-adults/malignant-brain-tumour-cancerous (23.27.2020).

10. Philips A, Henshaw DL, Lamburn G, et al. Authors' Comment on "Brain Tumours: Rise in Glioblastoma Multiforme Incidence in England 1995-2015 Suggests an Adverse Environmental or Lifestyle Factor". J Environ Public Health. 2018; 25;20;1-3.

11. Thust SC, Heiland S, Falini A, et al. Glioma imaging in Europe: A survey of 220 centres and recommendations for best clinical practice Eur Radiol. 2018; 28(8): 3306–3317.

12. Kamran N, Alghamri MS, Nunez FJ, et al. Current state and future prospects of immunotherapy for glioma Immunotherapy. 2018 Feb; 10(4): 317–339.

13. Patricia S. Targeting metastasis. Steeg Nat Rev Cancer. 2020 Mar 4.Nat Rev Cancer. 2016 Apr; 16(4): 201–218. doi: 10.1038/nrc.2016.25.

14. Stoyanov GS, Dzhenkov D, Ghenev P, et al. Cell biology of glioblastoma multiforme: from basic science to diagnosis and treatment. Med Oncol. 2018 Jan 31;35(3):27. doi: 10.1007/s12032-018-1083-x.

15. Stoyanov GS, Sarraf JS, Matev BK, et al. A Comparative Review of Demographics, Incidence, and Epidemiology of Histologically Confirmed Intracranial Tumors in Brazil and Bulgaria Cureus. 2018; 10(2): 2203; 2-8.

16. Abadin SS, Zoellner NL, Schaeffer M, et al. Racial/ethnic differences in pediatric brain tumor diagnoses in patients with neurofibromatosis type 1. J Pediatr. 2015; 167:613–620.

17. Cheng J, Meng J, Zhu L, et al. Exosomal noncoding RNAs in Glioma: biological functions and potential clinical applications Mol Cancer. 2020; 19: 66. Published online 2020 Mar 25. doi: 10.1186/s12943-020-01189-3.
18. Qie S, Li Y, Shi H, et al. Stereotactic radiosurgery (SRS) alone versus whole brain radiotherapy plus SRS in patients with 1 to 4 brain metastases from non-small cell lung cancer stratified by the graded prognostic assessment.A meta-analysis (PRISMA) of randomized control trials. Journal List Medicine (Baltimore) 97(33); 2018.
19. Batash R, Asna N, Schaffer P, et al. Glioblastoma Multiforme, Diagnosis and Treatment; Recent Literature Review. Curr Med Chem. 2017;24(27):3002-3009. doi: 10.2174/0929867324666170516123206.
20. Republic of Turkey Ministry of Health, General Directorate of Public Health, Turkey Cancer Statistics (Editors: Kara F, Keskinkılıç B) 2016, ISBN: Unpublished book data) Ankara, 2019 (data used with permission). March 2020.
21. Oktar N. High-Grade Glial Tumors. Temel Nöroşirürji, Vol. 1 (Editors: Korfalı E, Zileli M et al., Türk Nöroşirürji Derneği Yayınları No:10, Buluş Tasarım ve Matbaacılık, 1049-1056s, 2010, Ankara
22. Berkman MZ. Medulloblastom, PNET, Serebellar Astrositom, Ependimom, Hemanjioblastom. Editors: Korfalı E, Zileli M et al., Temel Nöroşirürji, Vol. 2, Türk Nöroşirürji Derneği yayınları No:10, Ankara, Buluş Tasarım ve Matbaacılık, 2010, 1057-1100.
23. Çobanoğlu S, Hamamcıoğlu MK, Metastatik Beyin Tümörleri. Editors: Korfalı E, Zileli M et al., Temel Nöroşirürji, Vol. 2, Türk Nöroşirürji Derneği yayınları No:10, Ankara, Buluş Tasarım ve Matbaacılık, 2010, 1117-1132.
24. Keleş E, Aydın S, Mandel NM et al., Düşük Dereceli Glial Tümörler. Editors: Korfalı E, Zileli M et al., Temel Nöroşirürji, Vol. 1, Türk Nöroşirürji Derneği yayınları No:10, Ankara, Buluş Tasarım ve Matbaacılık, 2010, 1019-1036.
25. Türkyılmaz M, Ministry of Health, General Directorate of Public Health, Head of Cancer Department, National Cancer Control Center data, January 2020.

2.15. Skin Cancer

Cancer statistics calculate how many people get cancer and die from cancer every year, how many people live after cancer diagnosis, and make classifications according to features such as age, gender, race, and geographic region. Although basal cell carcinoma, which constitutes 80-90% of skin cancers, is very frequently seen, it is very different from

other cancers since its mortality is very low and its 10-year survival rate is close to 100%. This situation prevents basal cell carcinoma from being evaluated together with other cancers. Basal cell carcinoma cases are excluded from the calculations when making cancer statistics, as it may cause imbalance in these calculations.

In the 2014 evaluations of the Turkish Ministry of Health, General Directorate of Public Health, Turkey Cancer Statistics, the top 10 most common cancers in Turkey, regardless of gender, are breast cancer, thyroid cancer, colorectal cancers, uterine cancer, gastric cancer, non-Hodgkin lymphomas, cervical cancer and pancreatic cancer respectively. But we know that the most common cancer in humans is skin cancer. The number of skin cancers diagnosed each year worldwide is higher than the number of all other cancers combined [1].

It is constantly emphasized that there is a noticeable increase in the incidence of skin cancer in the last 20 years. It is thought that at least 1 skin cancer will develop in one in five people by age 70. This increase in skin cancers is associated with a decrease in the atmosphere's ability to filter sunlight due to the thinning of the ozone layer and more ultraviolet radiation reaching the earth's surface as a result of this. In addition, the sun habits of the society are also changing. Sunbathing on the sunbeds by the sea or the pool, wearing clothes that do not cover the body and increasing interest in sports done under the sun such as jogging, tennis and swimming are thought to be among the reasons for the increase in skin cancer.

Sunburn, especially in childhood, has been identified as one of the most important risks for skin cancer to develop in the coming years [2]. Precisely for this reason, skin cancer is among the cancers whose incidence can be controlled at the highest rate with preventive measures. Because sun exposure is a completely modifiable risk factor [2]. It is important to implement sun protection before children reach the age of playing outside.

Skin cancers have a very high chance of early diagnosis. Because skin cancer is located in the skin and the entire skin can be seen with the naked eye. The only requirement for this is to undress. Skin cancers grow in front of our eyes. From this point of view, it can be thought that it may be easier to control skin cancer than other cancers. The biggest obstacle in front of this is the very low awareness of skin cancer in the society.

More than 95% of skin cancers are "***Non-Melanoma Skin Cancers***" and approximately 1-5% of them are "***Melanoma***". Although it accounts for only 1-5% of skin cancers, melanoma is responsible for approximately 90% of deaths due to skin cancer. Melanoma is the deadliest cancer of the skin. Early diagnosis of melanoma saves lives.

All other skin cancers except melanoma are examined under the heading “Non-Melanoma Skin Cancers”. Basal cell carcinoma and squamous cell carcinoma together constitute 95% of cancers in this group. In recent years, these two cancers are also named as "Keratinocyte Carcinomas" because they originate from keratinocytes in the epidermis layer of the skin. Both basal cell carcinoma and squamous cell carcinoma most commonly localize to the head and neck skin and progress with local destruction. They can also progress from the skin to the surrounding soft tissue, cartilage and bone tissue and destroy these tissues. Due to their destructive biological behavior, early diagnosis and appropriate treatment of basal cell carcinoma and squamous cell carcinoma, located especially in the nasal skin, ear skin, periorbital and perioral skin, are important. Early diagnosis and cure of these cancers can prevent loss of shape and function that may occur in very valuable organs such as the nose, eyes, ears and mouth. Basal cell carcinoma causes local disease with a rate of 99% and almost never metastasizes to regional lymph nodes and/or distant organs. On the other hand, squamous cell carcinoma with certain features can be fatal by making regional and distant metastases. This is particularly evident in immunosuppressed patients. Since squamous cell carcinoma is cancer that is seen 10 times more frequently compared to melanoma, its capacity to metastasize cannot be ignored. Therefore, the factors that increase the risk of metastasis of squamous cell carcinoma should be well known. It is also important to recognize actinic keratoses, which are the precursor lesion of squamous cell carcinoma, and to treat all of them appropriately.

Skin Cancer Risk Factors

As the 2 most important known risk factors for skin cancer, ultraviolet can be listed in the first place and phenotypic characteristics of the individual in the second place.

Ultraviolet causes skin cancer by causing DNA damage at the cellular level. In diseases in which some enzymes that repair DNA damage caused by ultraviolet are genetically deficient or absent (eg Xeroderma pigmentosum), skin cancers occur at a very early age. The natural source of ultraviolet is the sun. Apart from this, phototherapy devices used for treatment and solarium devices used for commercial purposes are also artificial sources of ultraviolet.

The phenotypic characteristics of the individual determine his/her sensitivity to ultraviolet. White-skinned individuals may develop sunburn in a shorter period of time than dark-skinned individuals. Therefore, individuals with light skin, blue, green or hazel eyes, red or blond hair, and freckles may develop ultraviolet damage more easily. Individuals carrying these phenotypic features are at higher risk for skin cancer.

Cutaneous Melanoma

Melanoma is a cancer that arises from melanocytes in the skin. Malignant proliferation of melanocytes forms melanoma. Bening proliferation of melanocytes, on the other hand, form nevi, which are popularly known as "moles". Therefore, moles and melanomas can look very similar clinically. Especially in their early stages, melanomas can be indistinguishable from an ordinary mole with the naked eye. Moles are the most common benign tumors in adults. Almost everyone has at least a few moles on their skin. For the early diagnosis of melanoma, it is important to know the features that distinguish melanoma from ordinary moles. In order to facilitate recall, a mnemonic consisting of the initials of the features that distinguish melanoma from me is used. ***ABCDE*** is a mnemonic for the English words Asymmetry_Border_Color_Diameter_Evolution, describing the features that distinguish melanoma from the mole. With this reminder, It is reminded that ordinary moles are symmetrical in color distribution and shape, while melanoma is asymmetrical in color and shape; while ordinary moles have regular borders, melanoma includes border irregularity; while ordinary moles are monochromatic, melanoma contains tan; while ordinary moles are usually less than 6 mm in diameter, melanomas are larger than 6 mm in diameter and while ordinary moles do not change, melanomas change and transform. This reminder serves for the early diagnosis of melanoma by providing ease of application for both individuals in the community, physicians and dermatologists. It is important for individuals in the society to understand that there may be a problem

with moles that are not similar to their other moles, look different from their other moles like an ugly duckling, are asymmetrical, have irregular borders, have more than one color, and change by growing. The fact that the frequency of melanoma is also increasing in our country makes it necessary to convey this information to our people.

The most important factor determining survival in melanoma is the thickness of the tumor. The thickness of the tumor is called the depth of invasion of the tumor or the Breslow thickness and is determined by the pathologist during microscopic examination. The measurement is made from the thickest part of the tumor, extending to the deepest part, by examining the entire tumor. Therefore, it is important to send the entire tumor to the pathologist for an accurate measurement. Under ideal conditions, total excision of the lesion with narrow margins is recommended when performing a biopsy with the suspicion of melanoma. The reason for performing total excision, especially with narrow surgical margins, is to prevent the deterioration of lymphatic drainage in the skin. If the suspected lesion is indeed a melanoma, it is important to perform the total excision for diagnosis with a narrow margin, in order to prevent the negative effects on subsequent tests to determine whether there is disease in the lymph node.

When the melanoma is still confined to the epidermis, it is called melanoma *in situ*, and in this case, the tumor thickness, or Breslow thickness, is considered zero. Melanoma *in situ* represents Stage 0 for melanoma. In stage 0 melanoma, 10-year survival is between 99-100%. Melanomas diagnosed with a Breslow thickness of less than 0.8 mm and without ulceration in the pathological examination are defined as Stage 1A and the 5-year survival is expected to be 97%. On the other hand, when the Breslow thickness increases, the probability of metastasis to the regional lymph node and distant organs increases, and the 5-year survival rates in metastatic disease decrease to as low as 20%. Images 1 and 2 show the melanoma observed on the scalp (Image 1) and metastasis in the postauricular lymph node (Image 2) of a patient, who was admitted to the hospital with the complaint of shortness of breath and who was diagnosed with diffuse melanoma metastasis in the lung as a result of detailed examination, and who was consulted by the Oncology Department to the Dermatology Department with the request to find the primary melanoma in the skin. The patient died shortly after diagnosis due to metastatic melanoma.

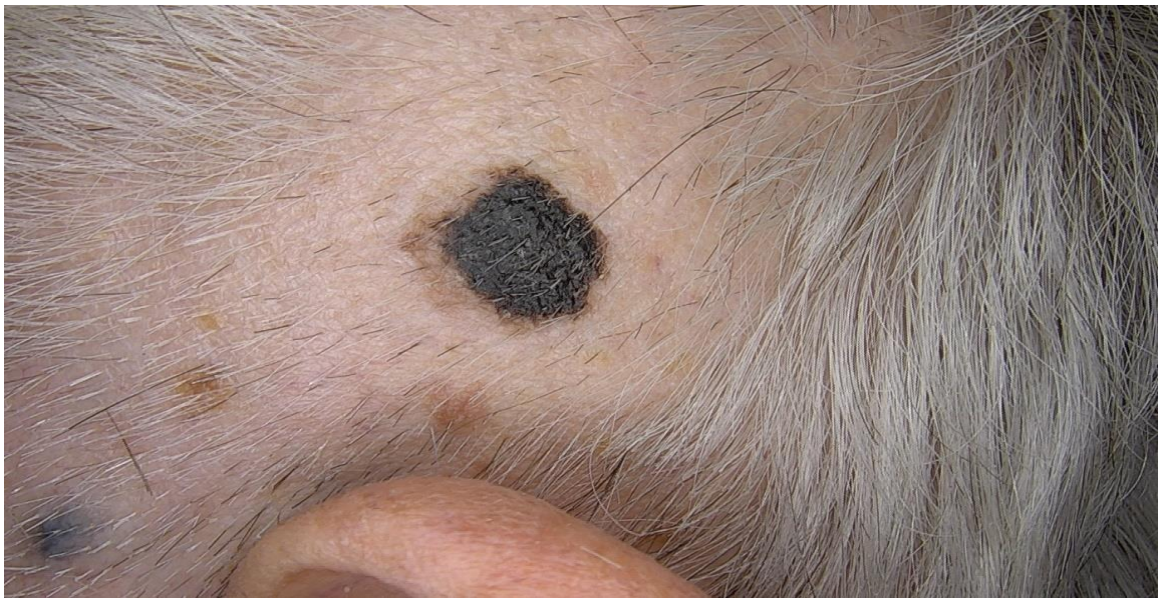


Image 1. Melanoma on the scalp

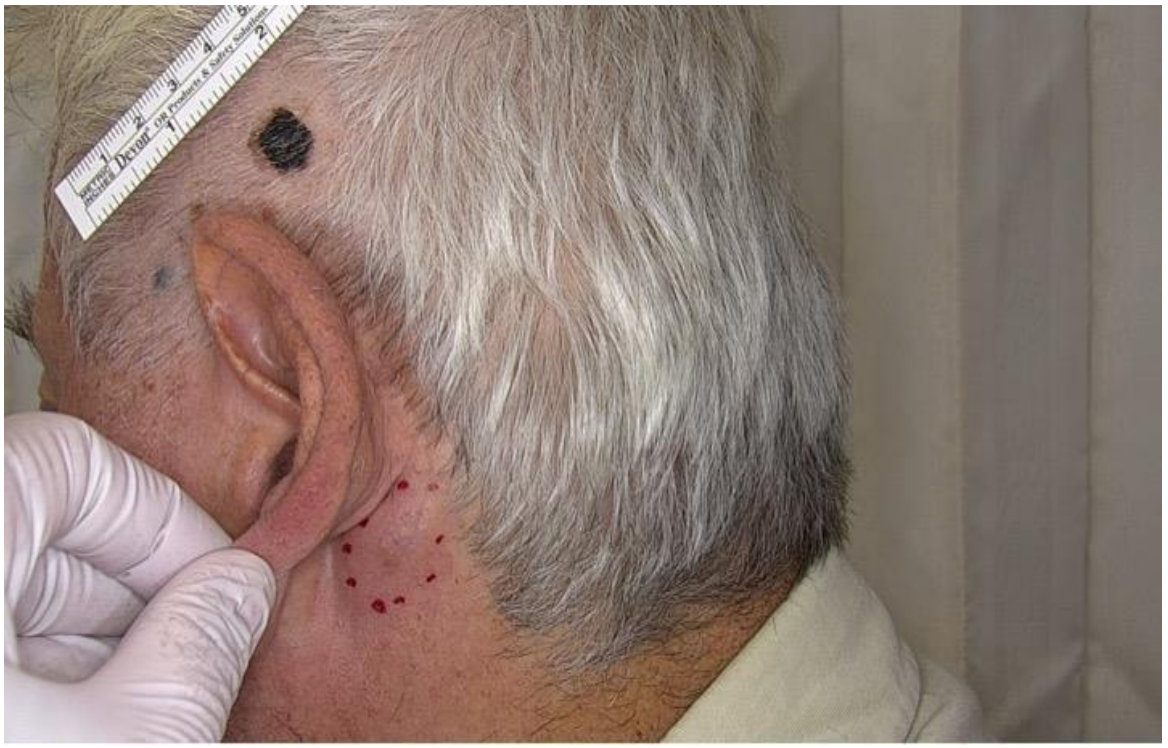


Image 2. Nodal metastases of melanoma

Basal cell carcinoma

It is the most common cancer in the world. Its frequency continues to increase. Its prevalence is predicted to continue to increase worldwide until 2040, due to populations that were not protected from the sun and were heavily exposed to ultraviolet

in the past. The incidence of basal cell carcinoma increases with age, and it doubles between the ages of 40 and 70. Basal cell carcinoma is more frequently seen in men. The disease is most common in the head and neck region. A slow-growing, non-healing and intermittently bleeding blister is the most common initial manifestation. Basal cell carcinoma is observed in the right ear helix in Image 3 (Image 3). Basal cell carcinoma is often seen as skin-colored or transparent, but basal cell carcinoma can also be observed in black color, not uncommonly, in individuals with dark skin, such as the people of our country. This clinical form, called pigmented basal cell carcinoma, is a condition that needs to be differentiated from melanoma.

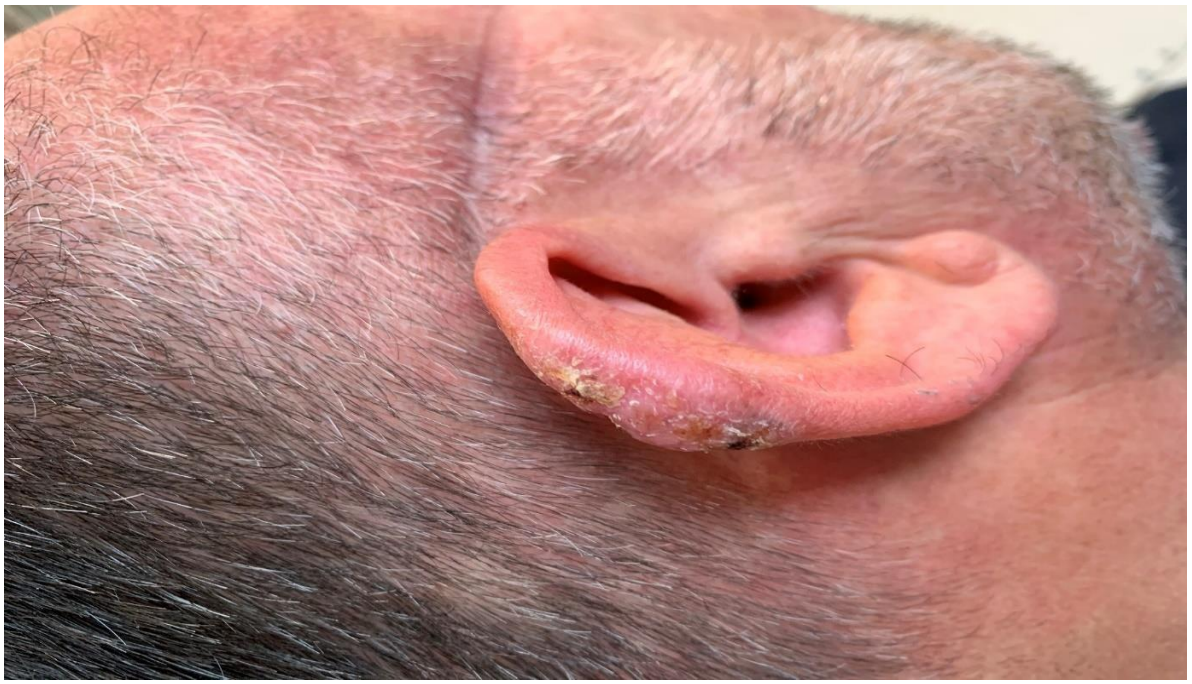


Image 3. Basal cell carcinoma of the ear helix

Basal cell carcinoma is not a fatal cancer. This skin cancer often settles around the nose, ears, eyelids and lips, causing tissue damage in these areas. If the diagnosis is delayed, tissue damage may develop at a level that will adversely affect the patient's quality of life. Its treatment is surgery. Surgery is curative. However, recurrence of basal cell carcinoma, especially in the head and neck, is not uncommon after surgical treatment. Recurrence of the cancer and the fact that the initial surgery is not curative occurs when the tumor cannot be completely excised. Basal cell carcinoma often spreads over a larger area than can be seen from the outside with the naked eye.

With this feature, it can be compared to an iceberg. Just as a tree has a trunk above the ground and roots below the ground, basal cell carcinoma has extensions under the skin. To achieve cure, it is important to excise the tumor with all its extensions. It is very difficult to apply the recommended surgical margins for curing without loss of function in basal cell carcinoma located on the face, especially around the nose, eyes, ears and lips. Mohs micrographic surgery is the gold standard treatment for high-risk basal cell carcinomas located in these areas [3].

Mohs Micrographic Surgery

It is a microscope-controlled surgical method used in the treatment of non-melanoma skin cancers, and melanoma in recent years [4]. While protecting the normal tissue at the highest rate, it provides the highest cure rates. This method, which allows all surgical margins to be examined under a microscope on a single slide, is actually not significantly different from standard excision surgically. Surgery is performed with narrow margins because Mohs surgery provides 100% microscopic margin control, eliminating the need for rambling safety margins. The step that makes the real difference in Mohs surgery takes place after excision, before microscopic examination and during macroscopy. At this stage, the lateral and deep surgical margins of the excised tissue are reduced to a single plane, color-coded, mapped and frozen in the frozen device after inversion. After this process, which takes place within minutes, if there is a tumor on the slide that is examined under the microscope, the process is repeated one more step only for the area where the tumor is observed. When no tumor is observed on the slide, it is understood that the tumor is removed from the skin with all its extensions and the surgical repair stage is started.

Cutaneous Squamous Cell Carcinoma

It is the second most common non-melanoma skin cancer, after basal cell carcinoma. It constitutes 20% of skin cancers. It is a cancer cured by surgical excision, but a group of cutaneous squamous cell carcinomas may end with local recurrence after surgery, metastasis and death. It is important to know the characteristics of this group, which is called aggressive quatnous squamous cell carcinoma.

The main 4 risk factors for cutaneous squamous cell carcinoma are ultraviolet, age, fair skin-colored eye phenotype and immunosuppression. Cutaneous squamous cell carcinoma is most frequently seen in men and in mid-60s. Solid organ transplant patients have a 65-250 times increased risk compared to the general population. Human papillomavirus (HPV) oncogenic types HPV 16 and HPV 18 play a role in the development of periungal and anogenital squamous cell carcinomas. [5] A periungal squamous cell carcinoma is seen in Image 4 (Image 4).

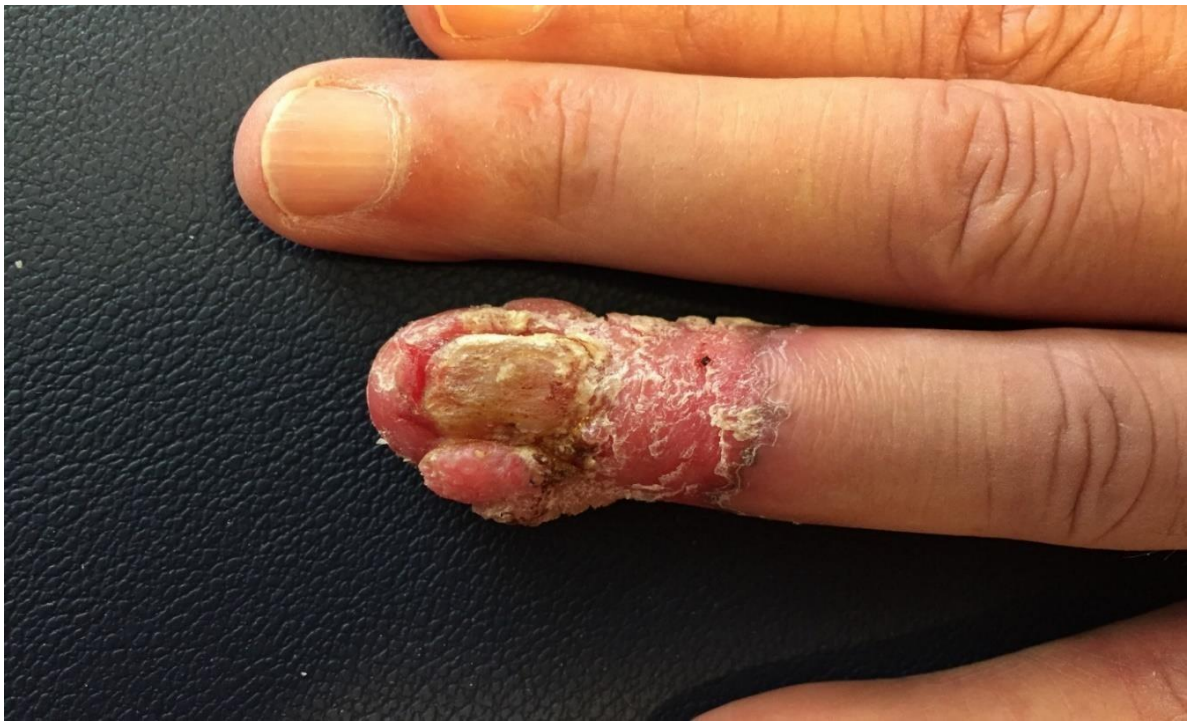


Image 4. Periungal squamous cell carcinoma

Disease-specific mortality is closely related to the tumor diameter greater than 2 cm at the time of diagnosis. The risk of nodal metastases and death is closely related to perineural invasion. Tumor thickness, local recurrence and metastasis are associated factors. Quatanous squamous cell carcinomas with tumor thickness greater than 2 mm have a 10-fold increased risk of local recurrence, whereas the risk of metastasis is increased 11-fold in tumors with tumor thickness reaching beyond the subcutaneous fat [5].

Actinic keratoses are precursor lesions for squamous cell cancer [6]. Chronic ultraviolet damage produces actinic keratoses, which is an intraepithelial neoplasia. Apart from the actinic keratoses, ultraviolet damage also affects the skin adjacent to the

actinic keratosis, this is named as area cancerization. Most actinic keratoses are cleared by the immune system, but in principle every actinic keratosis should be treated because some of them progress to invasive squamous cell cancer. Dermoscope is a useful method in the early diagnosis of both actinic keratoses and squamous cell cancer.

Dermoscopic Examination

Dermoscopic examination is a non-invasive diagnostic technique used in the diagnosis of skin diseases and is performed with an instrument called a dermoscope. This instrument basically consists of a focusable magnifying lens and a special illumination. It is the size of a hand and is used by bringing it close enough to touch the lesion to be examined on the skin. The dermatoscope allows morphological structures that cannot be seen with the naked eye to be observed in the horizontal plane from the epidermis to the papillary dermis. The macroscopic image that we see in the clinic, the structures observed with the dermoscope and the histopathological image that we examine under the microscope after the biopsy are different reflections of the same skin lesion and are in full correlation with each other. The identification of this correlation is almost revolutionary in dermatology and it forms a whole new field of study. The dermoscope has been an important part of the daily practice of dermatologists and offers the most obvious benefit in the early diagnosis of skin cancers. Dermoscopes have resulted in a significant reduction in the number of biopsies taken from lesions clinically suspicious for skin cancer [7]. It also made it possible to diagnose skin cancers at such an early stage that they would not even raise clinical suspicion. In this sense, dermoscopic examination provides a cost-effective skin cancer screening strategy.

Advances in technology made the development of digital dermoscopes possible. The digital dermoscope consists of a handheld dermoscope with a video camera, a monitor that projects the real-time image onto the screen and a computer system that lets the images to be stored and managed. The biggest advantage of digital dermoscopes, which are quite expensive systems, is that they make it possible to compare the dermoscopic images of the same lesion recorded at different times. In this way, changes in pigmented lesions which did not give sufficient clues in terms of melanoma in the first examination can be noticed and early diagnosis of melanoma can be achieved. Digital dermoscopes are also used for "mole mapping". Mole mapping is the process of

photographing all anatomical regions of the body with a camera and recording dermoscopic images of all melanocytic nevi in these areas with a digital dermoscope. This procedure, which is extremely labor-intensive, time-consuming, requiring physical strength and technical knowledge of the device, is an ideal method for the follow-up of melanoma patients with multiple melanocytic nevi.

Recommendations to control skin cancer

The best way to control skin cancer is early diagnosis. The biggest obstacle to early diagnosis in melanoma is that early melanomas resemble ordinary moles. The most distinctive feature that distinguishes melanoma from mole is that it changes slowly but steadily in size, colour, shape and symmetry. Our society should urgently be made to realize that it is necessary to go to the doctor for the "change mole". It is also important that our society learns to examine the skin so that people can recognize whether moles have changed. Individuals with more than 50 moles should know that they have a 10 times greater risk for melanoma. Patients with multiple moles should be followed up with a mole map, if there is a family history of melanoma. Preventing children from getting sunburn should be an important responsibility of parents and families should be informed about ways for protection from the sun.

Since basal cell carcinoma is a slow growing cancer, it is relatively advantageous in terms of early diagnosis. The most important factor that increases morbidity in basal cell carcinoma is local recurrences after treatment. Mohs Micrographic Surgery should be used in patients with indications.

It should be kept in mind that squamous cell carcinoma may be the cause of death in immunosuppressed patients, and early diagnosis and appropriate treatment of actinic keratoses should be provided in immunosuppressed patients. Protection from ultraviolet, which is the most important risk factor in skin cancers, should be taught to every member of the society and correct sun habits should be encouraged in the written and verbal media and social media.

Sun Protection

1. step: Sun protection prevents sunburn. Sunburn is a condition that creates a markedly increased risk for cutaneous melanoma. The easiest and shortest way to protect yourself from the sun is not to be under the sun when the sun is perpendicular. In our country, the sun is perpendicular to the earth between 10:00 and 16:00 in the summer months. It should be preferred to stay in the dark shadows instead of being under the sun at these hours. Umbrellas placed on the edge of sunbeds on the beach cannot create dark shadows and provide protection from the sun.

2. step: Sunlight cannot penetrate under tightly woven fabrics. Therefore, clothing provides protection from the sun. Long-sleeved blouses, shirts, and long-leg trousers are ideal clothing for sun protection. Since dark colors absorb light, the reflection of light that occurs in light colors does not happen with dark clothes. For this reason, especially dark blue, brown and black colors should be preferred for sun protection.

3. step: Accessories such as sunglasses, hats, gloves, scarves are very effective in protecting from the sun. It is important to use sunglasses especially at sunrise and sunset to block the sun that is perpendicular to the eye. When choosing a hat, care should be taken that its visor is at least 7 cm long and that the hat has a visor all around. Since basal cell carcinoma and cutaneous squamous cell carcinoma are especially located on the head and neck, it is important that the hat has a visor long enough to shade the nape, lateral sides of the neck, cheeks and ears.

4. step: In addition to the steps listed above that form the basis of sun protection, sunscreen creams also support sun protection.

RESOURCES

1. Guy GP, Machlin S, Ekwueme DU et al. Prevalence and costs of skin cancer treatment in the US, 2002–2006 and 2007–2011. Am J Prev Med. 2015; 48: 183–187.
2. Dowd MD.Treatment and Prevention of Pediatric Sunburn. Pediatr Ann. 2019; 48(6): e213- e214.
3. Bobotsis R, Guenther L. How Mohs surgery transformed into a first-line treatment for skin cancer. J Cutan Med Surg. 2017; 21(1): 40-41.

4. Ellison PM, Zitelli JA, Brodland DG. Mohs micrographic surgery for melanoma: A prospective multicenter study. J Am Acad Dermatol. 2019;81(3):767-774.
5. Que SKT, Zwald FO, Schmults CD. Cutaneous squamous cell carcinoma: Incidence, risk factors, diagnosis, and staging. J Am Acad Dermatol. 2018;78(2):237-247.
6. Fernandez Figueras MT. From actinic keratosis to squamous cell carcinoma: pathophysiology revisited. J Eur Acad Dermatol Venereol. 2017; 31: 5-7.
7. Thomas L, Puig S. Dermoscopy, digital dermoscopy and other diagnostic tools in the early detection of melanoma and follow-up of high-risk skin cancer patients. Acta Derm Venereol. 2017; 97: 14-21.

2.16. Epidemiology of

Childhood Cancer Types

Every year, around 277 thousand cancer patients are seen among children and young people in the 0-14 age group in the world. When 15-19 age group is included, this figure exceeds 300 thousand. While the incidence of cancer is 140.6 per million in the 0-14 age group, it is 185.3 in the 15-19 age group. One third of the most common tumors are leukemias, one fifth are brain tumors and 15% are lymphomas. Table 23 shows the data of the World Health Organization International Agency for Research on Cancer (IARC). It is seen that leukemias, brain tumors and lymphomas take the first three places in the data of the Ministry of Health and TPOG/TPHD data given in Figure 7 and Table 24.

Table 23. Age-Standardized Cancer Incidences and Number of Cases in Children in the World, IARC, 2018

Tumor type	**Incidence**	**number**	**%**
Leukemia	49.1	91.463	32.95
Lymphoma	15.5	30.410	10.96
CNS tumors	30.4	57.457	20.70
Sympathetic system tumors	10.9	19.235	6.92
Retinoblastoma	4.7	8.132	2.93
Renal tumors	8.3	14.871	5.36
Hepatic tumours	2.6	4.578	1.65
Bone tumors	5.7	11.597	4.18
Soft tissue sarcoma	9.1.	17.327	6.24
Germ cell/gonadal tumors	5.3	10.230	3.69
Epithelial tumors/Melanoma	5.1	10.332	3.72
Other and non-specific	1.1.	1.977	0.71

Table 24. Turkish Pediatric Oncology Group and Turkish Society Of Pediatric Hematology Distribution of Children's Cancer 2009-2019

Cancer	number	%
Leukemia	4.570	25.7
Lymphoma	3.477	19.5
CNS and spinal	2.493	14.0
Sympathetic system tumors	1.426	8.0
Retinoblastoma	348	2.0
Renal tumors	905	5.1
Hepatic tumours	304	1.7
Bone tumors	1.209	6.8
Soft tissue sarcomas	1.221	6.9
Germ cell tumors	1.165	6.6
Other epithelial and melanoma	533	3.0
Other and non-specific	119	0.7
Total	17.770	100

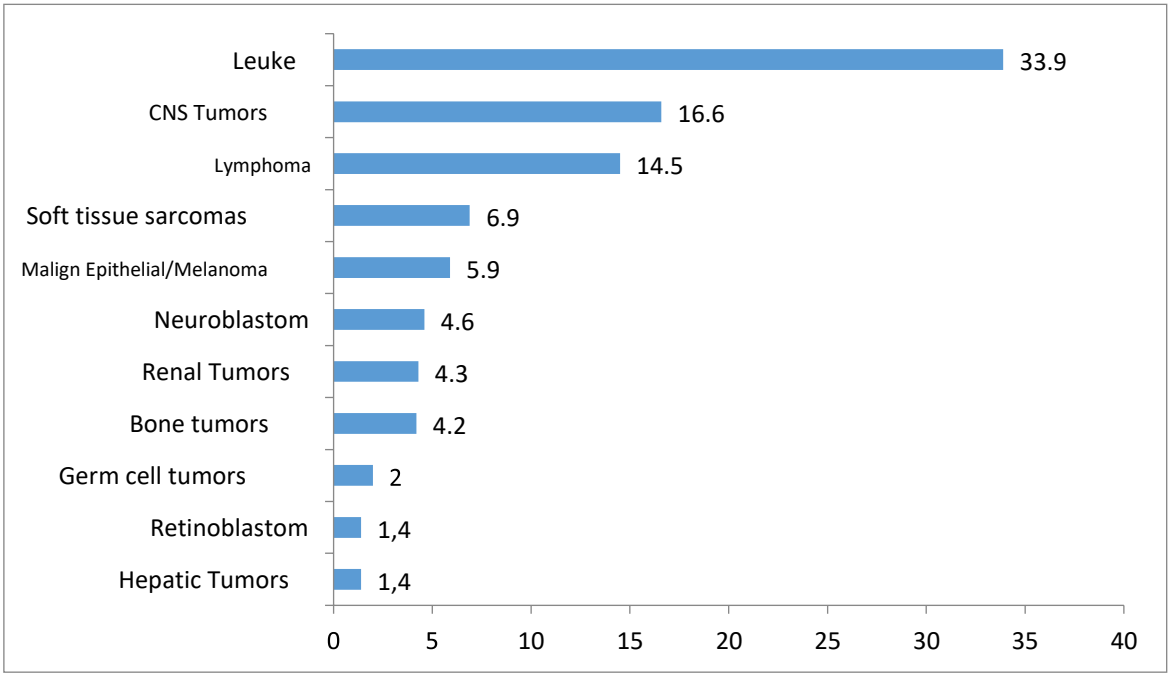


Figure 7. Percentage Distribution of Cancers in Children Aged 0-14 Group Within This Group (Turkey Compositional Data Base, 2016)(Other/Except for Unspecified Malignant Neoplasms)

Leukemias

Leukemias are the most common cancers in childhood. According to 2018 data of the World Health Organization (WHO) International Agency for Research on Cancer (IARC), 91463 cases were reported in the world in 2018, and they constitute one third (32.95%) of all cancers seen in childhood. In Turkey, leukemias constitute 25.7% of all childhood cancers according to 2009-2019 data of the Turkish Pediatric Oncology Group (TPOG) and Turkish Pediatric Hematology Association (TPHD),
and 33.9% according to the 2016 data of the Ministry of Health. Leukemia is defined as the presence of more than 25% of malignant hematopoietic cells called blasts in bone marrow aspiration. It develops as a result of uncontrolled clonal proliferation of a hematopoietic cell, the bone marrow is infiltrated by this cell group that proliferates uncontrollably, normal bone marrow function is impaired and bone marrow failure develops. Clinical features, laboratory findings and treatment responses differ according to leukemia types. Acute lymphoblastic leukemia (ALL) accounts for 77% of childhood leukemia, acute myeloid leukemia (AML) 11%, chronic myeloid leukemia (CML) 2-3%, and juvenile myelomonocytic leukemia (JMML) accounts for 1-2%. The remaining cases consist of a variety of acute and chronic

leukemias that do not meet the classical definitions of ALL, AML, CML, and JMML.

Acute Lymphoblastic Leukemia

Childhood acute lymphoblastic leukemia (ALL) is the most common childhood cancer, responsible for three-quarters of all childhood leukemia. It is the common name of a heterogeneous group of malignancies in which different underlying genetic anomalies lead to different clinical behavior and treatment responses. ALL classification is made according to the morphology of malignant cells in the bone marrow, the phenotype determined by measuring cell surface markers, and the cytogenetic and molecular genetic characteristics. B-lymphoblastic leukemia (precursor B-ALL or pre-B-ALL) accounts for 85% of ALL cases, T-lymphoblastic leukemia 15% and mature B cell leukemia about 1%. Mature B-cell leukemia is also called Burkitt's leukemia and requires a different treatment approach than other ALL subtypes. A small percentage of children with leukemia may have both lymphoid and myeloid origins. Chromosomal abnormalities are used to classify ALL into prognostic subgroups. Polymerase chain reaction (PCR) and fluorescent in situ hybridization (FISH) techniques enable the detection of molecular genetic anomalies and detect very small amounts of malignant cells (minimal residual disease [MRD]) at diagnosis and at follow-up. With the development of the DNA microchain technique, the expression of thousands of genes in leukemia cells can be examined. This technique will contribute to the understanding of the basic biology of ALL and the treatment approach.

Epidemiology

ALL is responsible for 25% of all cancers in children under the age of 15. Its incidence worldwide is 1:25000 per year, and 3,000 children are newly diagnosed each year in the United States. The most common age of diagnosis is 4, and 85% of patients are diagnosed between the ages of 2-10. It is more common in boys than girls in all age groups.

Etiology and Risk Factors

Although many genetic and environmental factors are associated with childhood leukemia, the etiology of ALL is not clearly known. GERMLINE MUTATIONS IN PAX5, ETV6, *and* TP53 GENES predispose to ALL, AND polymorphic variants in the

ARD5B, CDKN2A, and IKZF1 genes cause an increased risk of leukemia. In identical twins, if the first twin has leukemia, the risk of the second twin being sick is higher than the normal

population. If one of the twins is diagnosed with ALL in the first year of life and the twins share the same (monochionic) placenta, the risk is over 70%. Exposure to radiation, alkylating agents, epipodophyllotoxins, and benzene in the womb and childhood are associated with an increased incidence of ALL. It is also thought that there is a relationship between Epstein-Barr virus (EBV) infections and B-cell ALL (B-ALL).

Associated Diseases

Its incidence is increased in diseases such as ALL, Down Syndrome, Bloom syndrome, ataxia telangiectasia and Fanconi aplastic anemia, Diamond-Blackfan anemia, Kostmann syndrome, paroxysmal nocturnal hemoglobinuria, Li-Fraumeni syndrome.

Acute leukemia is observed 15-20 times more frequently in children with Down syndrome than in the normal population. When ALL develops in children with Down syndrome, the response to treatment is slightly worse than other children, this difference is due to the lack of good prognostic features such as ETV6-RUNX1 and trisomies and poor prognostic genetic anomalies such as IKZF1. Patients with Down syndrome have a severe sensitivity to methotrexate and other antimetabolites, so there is significant toxicity when given at standard doses. Therefore, treatment doses in patients with Down syndrome are adjusted with this in mind.

Symptoms and findings

The initial symptoms of ALL occur due to decreased bone marrow production, reduction of red blood cells (RBC), white blood cells (WBC), and platelets, or due to leukemic infiltration in extramedullary (outside the bone marrow) regions. There is usually weakness, malaise, irritability. Intermittent mild fever is often observed. Most patients present with bruises or paleness. In 1% of patients have musculoskeletal pain. Rarely, joint edema may occur. Bone pain is severe and may wake the patient up at night. As the disease progresses, bone marrow failure becomes evident with pallor, fatigue, exercise intolerance, bruising, oral mucosal bleeding or epistaxis, and fever due to infection or disease. Organ infiltration may lead to lymphadenopathy, hepatosplenomegaly, testicular enlargement, or central nervous system (CNS) involvement (cranial neuropathy, headache, seizure).

Hepatomegaly is present in 64% of patients and splenomegaly is present in 61% of patients. Lymphadenopathy is present in half of the patients, and may be localized or diffuse in the

cervical, axillary, and inguinal regions. In 1% of patients the testicles may enlarge unilaterally or bilaterally, secondary to leukemic infiltration. 'Superior vena cava syndrome' may develop due to compression of the mediastinal adenopathies on the superior vena cava. Due to collateral vein enlargement in the upper part of the chest, venous structures become prominent. The face may appear pletoric or the periorbital regions may appear edematous. A mediastinal mass may cause tachypnea, orthopnea, or respiratory distress. Leukemic involvement of cranial nerves may cause cranial nerve palsy and mild nuchal rigidity. Bleeding due to leukemic infiltration or thrombocytopenia may be seen in the optic fundus. Murmur, tachycardia and rarely congestive heart failure may be observed due to anemia.

Diagnosis

In ALL, there are peripheral blood findings indicating bone marrow failure. Anemia and thrombocytopenia are seen in most patients. The diagnosis should be confirmed by peripheral blood smear and bone marrow examination. Bone marrow aspiration and biopsy, flow cytometry, cytogenetic and molecular examinations are performed to confirm the diagnosis and classify the leukemia type. ALL is diagnosed when a >25% homogeneous lymphoblast population is detected in bone marrow examination. Lymphoblasts are typically two erythrocyte diameters, their cytoplasm is indistinct, and they are usually non-granular. Typically, their nuclei have no nucleolus or may have one small and indistinct nucleolus. Immunophenotyping of ALL blasts is performed by flow cytometry and precursor B-cell ALL, T-cell ALL and AML can be distinguished from each other. Approximately 5% of patients present with CNS leukemia, CNS involvement is defined as a white blood cell count >5/μL in the cytocentrifuge of the cerebrospinal fluid (CSF) and the presence of blasts in the specimen. The first LP should be performed by an experienced person because traumatic LP increases the risk of central nervous system (CNS) relapse. CNS involvement requires additional systemic and intrathecal treatment.

Recommendations for Early Diagnosis and Differential Diagnosis

Leukemia should be suspected in case of bone pain awakening from sleep in a child with complaints of weakness, loss of appetite and restlessness. Diagnosis can be made easily in these patients with anemia, thrombocytopenia and increased WBC in the blood count, and blasts in the smear and evaluation of the bone marrow. An increase in lactate dehydrogenase (LDH) is often a clue to the diagnosis of ALL. In the differential diagnosis, acute fever,

infectious mononucleosis with hepatosplenomegaly and lymphadenopathy, and fever, juvenile idiopathic arthritis, bone pain often without tenderness and joint edema should be considered. It is also important to distinguish it from other malignancies involving the bone marrow (such as AML, neuroblastoma, rhabdomyosarcoma, Ewing sarcoma and retinoblastoma).

Treatment

In ALL, significant improvement in overall survival has been achieved in recent years, thanks to multi-agent chemotherapy regimens. Survival rates vary depending on age and subtype. The current treatment approach is determined by taking into account some risk factors; age at diagnosis, WBC count at diagnosis, immunophenotypic and cytogenetic characteristics of the blast population, rate of early treatment response (eg, rate of clearance of leukemic cells from blood and bone marrow), and MRD assessment after induction therapy. Children under the age of one and over the age of ten and children with a leukocyte count >50,000/μL at diagnosis are considered high risk. Other factors that adversely affect the outcome are T-cell immune phenotype or slow response to initial therapy. Hypodiploidy, Philadelphia chromosome, and KMT2A (MLL) gene sequences indicate poor prognosis. Mutations in other genes, such as the IKZF1 gene, are associated with poor prognosis and may be important for future treatment algorithms. The most positive features are rapid response to treatment, hyperdiploidy, particularly trisomies (4, 10 and 17) and ETV6-RUNX1 (formerly TEL-AML1) sequences. A pre-B-cell ALL patient aged 1-10 years at diagnosis, with a white blood cell count below 50000/μL and without poor biological features (t(9;22) or 11q23 gene regulation) is defined as "standard risk". They would receive less intensified treatment than a “high-risk” patient with a white blood cell count greater than 50000/μL at diagnosis or aged 10 years or older. An infant younger than 1 year at diagnosis is considered very high risk and receives even more intensive chemotherapy. In addition, the treatment response of the patient evaluated with minimal residual disease (MRD) follow-up is also very important. With the risk-based treatment approach, early treatment intensification increases cure rates in patients with worse prognostic features, while treatment-related toxicity is minimized in patients with better prognostic features. In infants and patients with chromosomal abnormalities such as t(4;11), the risk of relapse is very high despite intensive treatment. Addition of BCR-ABL kinase inhibitor imatinib to chemotherapy in Philadelpiha chromosome positive t(9;22) ALL has been found to

dramatically improve prognosis. Event-free survival is increased by 30-70% with this approach.

Induction constitutes the first month of treatment, and at the end of induction, bone marrow aspiration is morphologically in remission in 95% of patients. The most commonly used drugs for induction include oral prednisone or dexamethasone, intravenous vincristine, daunorubicin, intramuscular or intravenous asparaginase, and intrathecal methotrexate.

The second phase of treatment is consolidation. Consolidation is followed by the intensification phase, which consists of several months of intensified chemotherapy. Maintenance therapy consists of daily oral mercaptopurine, weekly oral methotrexate, and often monthly intravenous vincristine and oral prednisone or dexamethasone pushes. Intrathecal chemotherapy is administered with methotrexate alone or in combination with cytarabine and hydrocortisone, usually every 2-3 months. The duration of treatment is 2.2 years for girls and 3.2 years for boys in the "COG" studies. ALL treatment is arranged according to prognostic factors or risk groups.

Hematopoietic stem cell transplantation is rarely used as a first line treatment for ALL because most patients can be treated with chemotherapy alone. Patients whose blasts show certain chromosomal abnormalities, hypodiploidy (<44 chromosomes) and patients who respond very slowly to treatment are more likely show better recovery rates to receiving stem cell transplantation from a human leukocyte antigen (HLA)-DR-matched sibling or fully matched unrelated donor than with intensive chemotherapy alone. Hematopoietic stem cell transplantation provides a cure in 50% of patients who relapse and go into remission with pre-transplant chemotherapy. Children who relapse 1 year after chemotherapy is completed (late relapse) can be treated with intensive chemotherapy without stem cell transplantation.

Some new biological agents, such as tyrosine kinase inhibitors and immunotoxin, are currently being investigated in chemotherapeutic studies in different research and development phases. Some of these treatments can be applied for future treatments in high-risk or relapsed patients. In addition, the addition of Imatinib, a tyrosine kinase inhibitor (TKI) developed against the Philadelphia chromosome (Ph+) protein product, to intensified ALL treatment in pediatric patients with Ph+ ALL was found to increase EFS in this patient group.

In the future, treatment may be tailored to the gene expression profiles of leukemic cells. In particular, the gene expression sequences induced by exposure to chemotherapy agents will help determine which patients have drug-resistant ALL. Successful results have been reported in the treatment of some patients with ALL relapses with chimeric antigen receptor (CAR) T-cell technology.

Prognosis

Significant improvement in survival rates has been achieved with advances in treatment, and according to current data, the standard risk EFS is around 90% in patients aged 1 to 10 years and with a leukocyte count below 50000/μL at diagnosis, while it is 88% in children aged 10 years and older. In addition, patients with hyperdiploidy in their blasts (with 50 chromosomes instead of 46), trisomies of chromosomes 4 and 10, and t(12;21) and ETV6-AML1 rearrangement in their blasts have a higher chance of cure than patients without these features, and EFS 95%- reached 97%.

However, survivors are more likely to have serious chronic health conditions such as musculoskeletal, cardiac, and neurological conditions than their siblings. In conclusion, long-term follow-up after ALL should be carried out in clinics where children and adolescents can be cared for and where are various specialists who can solve the difficulties that may be observed in this specific patient group.

Table 25. Effects of Chromosomal Abnormalities in ALL on Prognosis

CHROMOSOMAL ANOMALY	GENETIC CHANGE	PROGNOSIS
Trisomy 4, 10 and 17	-	Positive
t(12;21)	ETV6-RUNX	Positive
t(1;19)	TCF3-PBX1	None
t(4;11)	KMT2A(MLL)-AF4	NEGATIVE
t(9;22)	BCR-ABL	NEGATIVE
t(8;14)	IGH-MYC	None
Hyperdiploidy	-	Positive
Hyperdiploidy	-	NEGATIVE
t(10;14)	TLX1/HOX11	Positive
11q23	KMT2A (MLL) afresh regulations	NEGATIVE

Acute Myeloid Leukemia

The characteristic feature of AML is that >20% of bone marrow cells in sections prepared from bone marrow aspiration or biopsy contain blast cells with the early differentiation character of myeloid-monocyte-megakaryocyte series. In the current clinical approach, cell surface antigens are determined by flow cytometry and diagnosis is made with the help of chromosomal and genetic techniques. The WHO classification is used today. Immunophenotyping, cytogenetic and molecular analyzes are of increasing importance in confirming the diagnosis of AML and classifying it into biologically distinct subtypes with therapeutic and prognostic differences. Cytogenetic anomalies are seen in 80% of AML patients and usually indicate pronosis.

Table 26. WHO Classification of Acute Myelocytic Neoplasms

Acute myeloid leukemia with recurrent genetic abnormalities

- AML, t(8;21)(q22;q22.1); RUNX1-RUNX1T1
- AML, inv(16)(p13.1q22); CBFB-MYH11
- APL, PML-RARA
- AML, t(9;11) (p21.3;q23.3); MLLT3-KMT2A
- AML, t(6;9) (p23;q34.1); DEK-NUP214
- AML, inv (3) (q21.3q26.2) veya t(3;3)(q21.1;q26.2); GATA2, MECOM
- AML (megakaryositik), t(1;22) (p13.2;q13.3); RBM15-MKL1
- Temporary background: AML, BCR-ABL1
- AML, mutated NPM1
- AML, biallelic CEBPA mutations
- Temporary background: AML with mutated
- RUNX1 Myelodysplasia-associated changes

Treatment-related myeloid changes Acute myeloid leukemia, unless otherwise specified

- Less differentiated AML
- AML without maturation
- AML with maturation
- Acute myelomonocytic leukemia
- Acute monoblastic/monocytic leukemia
- Pure erythroid leukemia
- Acute megakaryoblastic leukemia
- Acute basophilic leukemia
- Acute panmyelosis and myelofibrosis

Myeloid sarcoma

Down syndrome associated myeloid proliferations

- Transient abnormal myelopoiesis
- Down syndrome associated myeloid

leukemia Blastic plasmacytoid dendritic cell neoplasm

AML, acute myelogenous leukemia; APL, acute promyelocytic leukemia.

Epidemiology

Acute myeloid leukemia (AML) accounts for 11% of childhood leukemias in the United States, with 370 children diagnosed each year. The incidence of AML increases in adolescence and constitutes 36% of leukemias among adolescents aged 15-19 years. AML is responsible for one-third of deaths from leukemia in children and adolescents.

Etiology and Risk Factors

Many chromosomal abnormalities associated with AML have been identified, but in most patients, a predisposing genetic or environmental factor could not be identified. Despite this, ionizing radiation, chemotherapeutic agents (alkylating agents, epidophyllotoxin), organic solvents are blamed in the etiology.

Associated diseases

The risk of AML is increased in Down syndrome, Fanconi anemia, Bloom syndrome, Kostmann syndrome, Shwachman-Diamond syndrome, Diaomod-Blackfan syndrome, Li-Fraumeni syndrome and Neurofibromatosis type 1 patients. AML in children with Down syndrome has much better outcomes, with a long-term survival of over 80%, than children with AML without Down syndrome. After induction therapy, these patients are treated with less intensity, providing excellent cure rates while reducing toxicity.

Symptoms and findings

Invasion of bone marrow with malign cells and secondary bone marrow failure as a result of this, cause the symptoms and signs of AML. Clinical findings of AML include anemia (44%), thrombocytopenia (33%), and neutropenia (69%). Findings may be minor, subtle, or life-threatening. The median hemoglobin value at diagnosis is 7g/dL and platelets are usually below 50000/μL. Often the absolute neutrophil count is below 1000/μL,

but at diagnosis, the white blood cell count is above 100000/μL in 25% of patients. In addition, patients with AML may have subcutaneous nodules or "blueberry muffin" lesions, gingival infiltration, diffuse intravascular coagulation findings and laboratory values (especially a sign of APL), and chloroma or granulocytic sarcomas, which are rare in ALL. These masses may occur without significant bone marrow involvement and are typically associated with the t(8;21) translocation. Chloromas can also be seen in the orbit and epidural space.

Hyperleukocytosis may be associated with life-threatening complications. Clustering of venous stasis and blasts in small vessels cause hypoxia, hemorrhage, and infarction, most notably in the lung and CNS. This clinical picture is a medical emergency and requires urgent intervention such as leukopheresis to lower the leukocyte count. CNS leukemia is found in 5-15% of patients at diagnosis, and this rate is higher than the rate of CNS involvement at the time of diagnosis in ALL patients. Meningeal infiltration is more common in some subtypes such as M4 and M5 than in other subtypes. In addition, clinically significant coagulopathy can be seen in the diagnosis of M3, M4 or M5 subtypes. This problem may be detected by bleeding or by an abnormality in the scan for disseminated intravascular coagulation and should be partially corrected prior to treatment, as treatment will increase the coagulopathy, albeit transiently.

Diagnosis

Examination of bone marrow aspiration and biopsy in patients with AML typically reveals hypercellular bone marrow containing one type of cell. Flow cytometry and special staining allow detection of cells containing myeloperoxidase. Some chromosomal abnormalities and molecular genetic markers are characteristic for certain subtypes.

Treatment

AML is less responsive to treatment than ALL and requires more intensive chemotherapy. Treatment-related toxicity is common and can be life-threatening, so treatment is recommended only in tertiary oncology centers.

There are many different induction chemotherapy protocols, typically involving a combination of anthracyclines and high-dose cytarabine. Targeted therapies for genetic markers may be helpful). 5% of patients die from infection or bleeding before remission is

achieved. Post-remission therapy is selected based on both the combined cytogenetic and molecular markers of leukemia and response to induction therapy (MRD assessment). In selected patients with positive prognostic characteristics [t(8;21); t(15;17); inv(16)] and good results with chemotherapy alone, stem cell transplantation is recommended only after relapse. However, stem cell transplantation is recommended after first remission in patients with adverse features (eg, monosomy 7 and 5, 5q- and 11q23 anomalies) who have had worse outcomes after chemotherapy. Thanks to advances in supportive care, there is no longer a significant difference in mortality in matched comparisons in AML patients with and without stem cell transplant.

Acute promyelocytic leukemia characterized by gene rearrangement involving the retinoic acid receptor [t(15;17); PML-RARA)] responds very well to the combination of all-trans-retinoic acid (ATRA, retinoin) with anthracycline and cytarabine. Success of treatment in patients with this disease eliminates the need for bone marrow transplantation after the first remission. Arsenic trioxide is an effective non-toxic treatment for APL. Adult studies of combined ATRA/arsenic initial therapy without toxic drugs in APL are promising and support new protocol studies in children. More supportive treatment is needed in patients with AML because the intensive treatment they receive causes long-term bone marrow suppression and a high incidence of serious infections, especially viridans streptococcal sepsis and fungal infection. These patients may require prolonged hospitalization, filgrastim (granulocyte colony stimulating factor) and prophylactic antimicrobials.

Prognosis

The prognosis varies according to the AML subtype. Currently, AML patients with t(8,21), t(15;17), inv16 and Down syndrome have the best prognosis, with long-term survival rates of 65-75% with chemotherapy. The worst outcomes are seen in AML patients with monosomy 7 or 5, 7q, 5q-, 11q23 cytogenetic abnormalities, or FLT3 mutation or Internal tandem duplication. Aggressive multi-agent chemotherapy induces remission in approximately 85-90% of patients. Survival has increased dramatically to 60-70% with today's modern treatment methods.

According to the results reported from different centers, 5-year survival rates after the first remission in patients who do not have a fully compatible sibling donor for stem cell transplantation vary between 50-60%. This rate is slightly better in those with fully matched

sibling donors, with a 5-year survival of 60-70% after allogeneic stem cell transplantation.

Table 27. Effects of Common Chromosomal Abnormalities in AML on Prognosis

CHROMOSOMAL ANOMALY	GENETIC CHANGE	PROGNOSIS
t(8;21)	RUNX1-RUNX1T1	Positive
inv(16)	CBFB-MYHII	Positive
t(15;17)	PML-RARA	Positive
11q23 anomalies	KMT2A(MLL) rearrangements	NEGATIVE
FLT3 mutation	FLT3-ITD	NEGATIVE
del(7q), -7	Unknown	NEGATIVE

Chronic Myeloid Leukemia

Chronic myeloid leukemia (CML) is a clonal disorder of hematopoietic tissue that accounts for 2-3% of childhood leukemias. Approximately 99% of cases are characterized by the t(9;22) (q34;q11) translocation resulting in the BCR-ABL2 fusion gene, also known as the Philadelphia chromosome.

The presenting symptoms of CML may include fever, fatigue, weight loss, and anorexia. There may be pain due to splenomegaly. An increased white blood cell count and the presence of cells from all stages of differentiation in the entire myeloid series in the peripheral blood and bone marrow suggest the diagnosis. Demonstration of the characteristic Philadelphia chromosome and BCR-ABL gene sequence by cytogenetic and molecular studies confirms the diagnosis. Although this translocation is characteristic of CML, it can be found in a small percentage of patients with ALL.

The disease is characterized by an increased leukocyte count in which the mature form formed by the malignant clone is predominant, as well as the first chronic phase characterized by increased immature granulocytes. In addition to leukocytosis, mild anemia and thrombocytosis may be present in the blood count. Typically, 3-4 years after onset, the chronic phase ends and CML progresses to an accelerated or 'blast crisis' phase. At this point, the blood count increases dramatically and the clinical picture is indistinguishable from acute

leukemia. Additional findings such as increased blood viscosity from hyperleukocytosis and neurological symptoms resulting from decreased CNS perfusion may be observed.

Imatinib, an agent designed to inhibit BRC-ABL tyrosine kinase, has been used in adults and children and has been shown to produce a major cytogenetic response in over 70% of patients. Experience in children shows that it can be used safely at a level comparable to that in adults. Second-generation tyrosine kinase inhibitors, such as dasatinib and nilotinib, have increased remission rates in adults and have been added to first-line treatment protocols for this population. While waiting for a response to the tyrosine kinase inhibitor, dysfunctional and life-threatening symptoms and signs of CML can be controlled with hydroxyurea, which gradually reduces the leukocyte count to normal. The standard approach for CML in children is treatment with a tyrosine kinase inhibitor.

Juvenile Myelomonocytic Leukemia

Juvenile myelomonocytic leukemia (JMML) is a rare clonal disorder of hematopoietic stem cells. It constitutes 1% of childhood leukemias. JMML patients present with rash, lymphadenopathy, splenomegaly, and hemorrhagic findings. In the examination of peripheral blood, anemia is detected in the presence of increased leukocyte count, increased monocytes, thrombocytopenia and erythroblasts. The bone marrow has a myelodysplastic appearance and blasts make up less than 20% of all cells. Most JMML patients have NRAS, NF1 and PTPN11 mutations that activate the RAS oncogene pathway. Patients with neurofibramatosis type 1 and Noonan syndrome are predisposed to this type of leukemia. Although stem cell transplantation is the best chance for cure in most patients with JMML, the prognosis is poor, with survival rates less than 30%.

Lymphomas

It is one of the most common tumors in children. According to the 2018 data of the World Health Organization (WHO) International Agency for Research on Cancer (IARC), 30410 lymphomas were reported in the world in 2018, and it ranks third after leukemia and brain tumors with 10.96%. According to the 2009-2019 data of the Turkish Pediatric Oncology Group (TPOG) and the Turkish Pediatric Hematology Society (TPHD), it ranks second with 19.5%, while it ranks third with 12% according to the 2016 data of the Ministry of Health. This may be related to the fact that low-grade brain tumors are not referred to pediatric

oncology centers. Lymphomas are examined under two groups.

Hodgkin Lymphoma (HL) ***Epidemiology***

It constitutes 6-8% of all pediatric tumors. It constitutes up to 40% of lymphomas. It is rare under the age of five, it is more common in adolescents. While it is more common in males at early ages, there is no significant difference in adolescents. Histopathological subtypes of classic Hodgkin lymphoma are nodular sclerosing, mixed cell, lymphocyte-rich and lymphocyte-poor groups. The other main group is the nodular lymphocyte-rich group and constitutes 10% of Hodgkin lymphomas.

Etiology and Risk Factors

Its etiology is not fully understood. Epstein Barr virus is known to be associated, at least in some cases. In classic Hodgkin lymphoma, familial cases constitute up to 4% of all cases.

Symptoms and findings

The main symptom is painless supraclavicular or adenopathy in the cervical region. Two-thirds of patients have varying degrees of involvement of mediastinal lymph nodes. They also come with large mediastinal masses. Abdominal involvement is rare. Depending on the area of involvement, signs and symptoms may be associated with compression. Systemic symptoms may also occur. B symptoms are related to prognosis and consist of unexplained fever exceeding 38 degrees, weight loss of more than 10% of body weight in the last 6 months, night sweats that are intense enough to change clothes.

Itching is another common finding in HL. The Ann Arbour staging system is used for staging.

Diagnosis

In the history, the existence of adenopathy, its whereabouts, systemic symptoms and presence of B symptoms are questioned. In the physical examination, the location, size, symmetry, symmetricalness, whether it is painful, whether the liver spleen is enlarged or not, and lung listening findings are the leading findings that need attention. Laboratory examinations include complete blood count, liver and kidney function tests, sedimentation, and CRP tests. Imaging methods are performed by planning on a case-by-case basis, such as

ultrasonography, CT, MRI, PET CT. Bone marrow biopsy is performed in cases considered advanced. Definitive diagnosis is made by biopsy.

In the differential diagnosis, non-tumor causes of lymphadenopathy (infection and non-infectious causes), non-Hodgkin lymphomas, less commonly nasopharyngeal cancer, soft tissue tumors and other tumors should be kept in mind.

There are no recommendations for early diagnosis and screening. It is important to prevent delays in diagnosis and treatment through regular examinations of healthy children and adolescents and awareness of families.

Treatment and prognosis

Chemotherapy and radiotherapy are used in treatment. Radiotherapy is used in advanced stage patients and patients who do not respond well to treatment in the early stages. In chemotherapy, protocols such as MOPP, COPP, ABVD, OPPA, OEPA and their combinations are used in the historical development process. Long-term treatment success is over 90%. The late effects of treatment should be carefully monitored. Long-term follow-up is recommended for cardiac and pulmonary effects, endocrine effects, and secondary cancers.

Non-Hodgkin lymphoma (NHL)

Childhood Cancer Types

It constitutes up to 7% of all pediatric cancers. It is more common than Hodgkin lymphoma. It is less common under the age of five. It is more common in the 5-10 year old group. It is 3-4 times more common in boys than girls. They originate from immature or mature B, T and Natural killer cells. The main histopathological subtypes are given below.

Histopathological subtypes

- Precursor lymphoid tumors
    - T-lymphoblastic lymphoma 15-20%
    - B lymphoblastic lymphoma 3%
- Mature B-cell lymphomas
    - Burkitt lymphoma 35-40%
    - Diffuse large cell lymphoma 15-20%

    - Primary mediastinal B-cell lymphoma 1-2%
    - Pediatric follicular lymphoma Rare
    - Pediatric nodal marginal zone lymphoma Rare
- Mature T cell lymphomas
    - Anaplastic large cell lymphoma. 15-20%
    - Peripheral T-cell lymphoma Rare

Etiology and risk factors

Etiology is unknown. The relationship between Burkitt lymphoma and EBV is more evident, especially in cases seen in Africa. Lymphomas are also more common in some immunodeficiencies.

Symptoms and findings

Although signs and symptoms differ in different histopathological subtypes, they consist of diffuse lymphadenopathy/mass and associated signs and symptoms especially in the neck, mediastinum, abdomen. Among mediastinal cases, superior vena cava syndrome due to mass compression, compression findings in the presence of abdominal and thoracic acid, metabolic/biochemical disorders and tumor lysis syndrome are important in cases where the tumor volume/burden is high. If there is bone marrow involvement, related signs and symptoms develop. Systemic symptoms such as fever and weight loss may also occur. St Jude staging system is used in staging.

Diagnosis

Signs and symptoms related to adenopathy and mass, and compression findings are carefully questioned from the history. In the examination, findings regarding the location, size, neighborhood, extent, presence of ascites/effusion, bone marrow and central nervous system involvement are carefully examined. Hodgkin lymphoma, other lymph node involvement diseases and other tumors according to the area of involvement should be considered in the differential diagnosis.

Patients with suspected non-Hodgkin lymphoma should be consulted without delay with a pediatric oncologist/hematologist because of the potential for rapid growth of the tumor. Compression findings and presence of tumor lysis syndrome require urgent

intervention and treatment.

Laboratory examinations include complete blood count, liver and kidney function tests, sedimentation, CRP, LDH tests. Imaging methods are performed by ultrasonography, CT, MRI, and case-by-case planning. Bone marrow aspiration is required for staging. Definitive diagnosis is made by biopsy. Ascitic fluid, bone marrow, CSF examinations, immunophenotype determinations in both fluids and tissues are important.

Treatment and prognosis

Risk groupings are made according to tumor subgroups and stage, and treatment plans are made accordingly. LMB and BFM protocols in B-cell lymphomas are the protocols used according to the preference of the centers. In recent years, the duration of treatment in B-cell lymphomas has decreased to 6 months in advanced stages. In advanced cases, rituximab is recommended. Treatment success has exceeded 90%. In T-cell lymphomas, BFM-weighted protocols have come to the fore, and treatment success has exceeded 85%.

Brain Tumors

Childhood Cancer Types

Brain tumors are the most common solid tumors of childhood. According to the 2018 data of the World Health Organization (WHO) International Agency for Research on Cancer (IARC), 57457 cases were reported in the world in 2018, and it ranks second after leukemia with 20.7%. 1500-2000 children are newly diagnosed each year in the United States. According to the 2009-2019 data of the Turkish Pediatric Oncology Group (TPOG) and the Turkish Pediatric Hematology Society (TPHD), it ranks third in our country with 14%, while it ranks second with 18.3% according to the 2016 data of the Ministry of Health. Brain tumors are the most common cause of death from cancer in children under the age of 14. It is more common among men.

Classification

WHO updated the classification of central nervous system tumors in 2016, and according to the new classification, tumors were classified not only according to their histopathological features, but also considering molecular parameters. Gliomas constitute half of brain tumors in children and adolescents. Astrocytomas and ependymomas are in this group. Medulloblastoma is one of the most common malignant brain tumors in children, accounting for 6-7% of all brain tumors. ATRT and PNET constitute embryonal brain tumors other than medulloblastoma. Pituitary tumors and craniopharyngioma develop in the sellar region. Neuronal or mixed neurono-glial tumors are responsible for 7% of all brain tumors. Germ cell tumors located in the pineal and suprasellar regions can be seen in 3-4 percent of cases. Up to 60% of brain tumors in children are located supratentorially. Spinal placement is seen in 8% of brain tumors.

Etiology and risk factors

Some patients have a genetic predisposition. New generation sequencing revealed an underlying genetic mutation in 8% of brain tumor patients. Susceptibility to brain tumors is increased in neurofibromatosis, tuberous sclerosis, Von Hippel Lindau, Gorlin, Turcot and Li Fraumeni syndrome. In addition, exposure to ionizing radiation has been shown to increase the risk of brain tumors. All patients with glioma and meningioma should be screened for NF-1. Neurofibromatosis type 2 and Von Hippel Lindau syndrome should be considered in children with meningioma who do not have skin manifestations of NF-1. Inherited germline mutations can be seen in atypical teratoid rhabdoid tumors (ATRT) and choroid plexus carcinomas. In these tumors, family history should be taken into account and genetic counseling should be given.

Symptoms and findings

Clinical findings in diagnosis vary according to the age of the child and the location of the tumor. The classic triad of morning headache, vomiting and papilledema is present in less than 30% of patients at the time of diagnosis. School failure and personality changes are common in older children. Irritability, growth and developmental retardation are common in young children with brain tumors. Newly developed head tilt may be caused by a posterior fossa tumor. Infratentorial tumors are more common in children younger than two years of

age. These children usually present with nonspecific findings such as vomiting, imbalance, lethargy and irritability. Macrocephaly, ataxia, hyperreflexia, cranial nerve palsy can be seen. In tumors involving the optic nerve pathway, such as optic glioma, ocular findings such as the inability to trace a finger and visual disturbances can be seen. Optic glioma in young children is often associated with neurofibromatosis.

In older children, supratentorial tumors are more common and cause headache, visual disturbances, seizures, and focal neurological symptoms. The presenting findings are usually nonspecific. School failure personality changes are often frequent. Headache is common and can be confused with migraine. Older children with infratentorial tumors usually present with signs and symptoms of hydrocephalus such as progressive worsening of morning headache, vomiting, unsteady gait, diplopia, and papilledema. Cerebellar astrocytomas grow slowly and symptoms worsen over months.

Posterior fossa ependymomas originate from the vomiting center near the 4th ventricle and morning vomiting may be the only finding. Children with brain stem tumors may present with facial and extraocular muscle palsies, ataxia and hemiparesis, and hydrocephalus is present in 25% of the patients.

Diagnosis

Magnetic resonance imaging (MRI) is the preferred diagnostic method for pediatric brain tumors. Diagnosis is made by tumor biopsy, spinal imaging studies are also used to investigate whether there is spread. In cases where biopsy cannot be taken in tumors of regions such as brain stem and pons, radiological diagnosis can also be made. In order to evaluate the residual after tumor resection, imaging should be performed within 48 hours after surgery to avoid changes due to surgery. Spinal imaging and CSF cytology should be performed while investigating the involvement areas in the diagnosis of medulloblastoma, ependymoma, and pineal region tumors. Spinal MRI should be performed in all children prior to surgery for midline tumors of the fourth ventricle or cerebellum. The CSF sample should be taken at the time of diagnostic surgery or, if this is not possible, 7-10 days after surgery. Beta human chorionic gonadotropin (β-HCG) and alpha-fetoprotein (AFP) should be measured in blood and CSF in all pineal and suprasellar tumors.

Treatment and prognosis

Low-grade astrocytomas are cured in most cases by complete surgical excision only. In low-grade astrocytomas, chemotherapy is 40-50% effective, at least helping to delay radiotherapy even when it is not helpful. In children, the long-term survival percentages in tumors that diffusely infiltrate the brain stem and primarily involve the pons (diffuse intrinsic pontine gliomas) are below 5%. Brain stem tumors are often treated without tissue diagnosis. The preferred initial approach for all tumors is to excise the tumor as widely as possible. In cases where the tumor cannot be surgically removed initially, second-look surgery is increasingly used after chemotherapy. The prognosis is good for low grade and completely removed tumors. In tumors with a high risk of neural axis involvement (such as medulloblastoma), craniospinal irradiation is still the standard treatment approach in children over 3 years of age. There are ongoing studies to reduce the dose of craniospinal irradiation for tumors such as medulloblastoma. Since radiotherapy can cause significant neuropsychosocial, intellectual and endocrinological sequelae in young children, it is not used in children under 3 years of age, which negatively affects the prognosis in some patients. Chemotherapy is effective in the treatment of low-grade tumors, malignant astrocytoma, and medulloblastomas. The most exciting development in pediatric neurooncology is the identification of biological and clinical subtypes of medulloblastoma and ependymoma. Molecular studies have also gained momentum in glial tumors. Thanks to this development, it will be possible to use new generation target therapies according to these determined biological subtypes.

Neuroblastoma

Childhood Cancer Types

It is the most common extracranial solid tumor of childhood. It originates from the precursor cells of the sympathetic system, neural crest cells. It constitutes about 8% of all childhood tumors. According to the IARC database in 2018, the number of cases seen in the world was 19,235, constituting 6.92% of all childhood cancers. Among the childhood cancers, it constitutes 5% of the data of the Ministry of Health and 8% according to the data of TPOG/TPHD. Neuroblastoma is the most undifferentiated form, the more differentiated form is ganglioneuroblastoma and the benign form is ganglioneuroma. Pheochromocytoma and paraganglioma seen in adults are extremely rare in children.

Although it is seen slightly more in men (1.2 times), the difference is not very obvious. It is most common around 2 years of age. It is seen 36% of under 1 year old, 80% of under 4 years old, 97% of under 10 years old.

Etiology and risk factors

Etiology is unknown. It is known to be associated with diseases such as neurofibromatosis, Hirshsprung's disease. Amplification of the N-myc oncogene and deletion of 1p36 are the most known genetic changes. Familial cases constitute 1-2% of all cases.

Symptoms and findings

65% of the cases are in the abdominal location (35% surrenal, 30% extra-surrenal), 20% are thoracic, the rest are in the pelvic, cervical and other locations. The signs and symptoms vary according to the location of the primary tumor and the presence of metastases. Detection of mass in the upper quadrants in abdominal cases, pain and palpable masses in bone metastases, cranial masses due to involvement of the skull bones, “racoon eye” appearance due to involvement of orbital bones, skin findings, neurological findings due to compression if it has entered the spinal canal in abdominal or thoracic cases, decreased strength/ loss, urinary and defecation problems may occur. If there is bone marrow involvement, related signs might develop. Symptoms and signs such as fever, pain, pallor, weight loss, and loss of appetite are seen. Paraneoplastic syndromes are persistent diarrhea and the presence of opsomyclonus. In upper thoracic and cervical cases, Horner's syndrome is seen due to involvement of the sympathetic ganglia. It can also be detected on X-rays taken for other reasons, especially in thoracic cases. The International Neuroblastoma staging system is used for staging. Stage 4S is a neuroblastoma-specific condition, local stage I-2, and the prognosis is good despite metastatic disease such as limited bone marrow (less than 10%), liver, and skin involvement.

Diagnosis

The mass, pain, fever, compression findings, neurological signs and symptoms arising from the primary mass and its metastases suggest the disease. In the differential diagnosis, Wilms tumor, liver tumor and other tumors should be kept in mind in abdominal cases.

With imaging methods such as direct radiographs, bone survey, ultrasonography, CT and MRI, evaluations such as location, size and presence of compression of tumors and metastases are made. Diagnosis is made by biopsy, but methods such as vanil mandelic acid in the urine (VMA), bone marrow aspiration (in terms of involvement and presence of rosettes) are performed in each patient. The extent of the disease and bone involvement are evaluated with MIBG scintigraphy.

Treatment and prognosis

Neuroblastoma is treated with surgery and chemotherapy in the early stages and in newborns in special cases, except for a limited number of patients followed up with a watch-see policy in appropriate cases. It is resected in those who are resectable at the time of diagnosis, but in large, risky cases with resection, reduction with chemotherapy and then surgery is applied. In the presence of residual disease, radiotherapy is applied. Bone marrow transplantation can be applied in selected advanced cases. In most protocols, the differential drug retinoic acid is added to the treatment. It is between 90-100% in early stages and 10-50% in stage III-IV cases. In recent years, survival has been increased by 15-20% in advanced cases with targeted anti-GD2 antibodies. N-myc amplification, 1p deletion, age (over 18 months), advanced stage are poor prognostic factors. Early diagnosis is important as the chance of survival is higher in the early stages.

Retinoblastoma

According to the 2018 data of the World Health Organization (WHO) International Agency for Research on Cancer (IARC), 8132 retinoblastoma cases were reported in the world in 2018, accounting for 4.7% of all pediatric cancer cases. According to the 2009-2019 data of the Turkish Pediatric Oncology Group (TPOG) and the Turkish Pediatric Hematology Association (TPHD), it constitutes 2% of all childhood cancers in our country, and 1.3% according to the 2016 data of the Ministry of Health.

Childhood Cancer Types

Retinoblastoma originates from embryonic retinal cells. It is the most common intraocular tumor in children and accounts for 5% of the causes of childhood blindness. It is a tumor of early childhood and 90% is diagnosed before the age of 5 years. 20-30% of children have bilateral involvement at diagnosis and are typically diagnosed earlier (average

age 14 months). In contrast, unilateral disease is diagnosed in an average of 23 months.

Etiology and risk factors

Retinoblastoma is the prototype of hereditary cancers linked to the retinoblastoma gene (*RB1*) and is localized on the long arm of chromosome 13 (13q14). It is known as a tumor suppressor gene and controls cell growth. Uncontrolled cell growth leads to tumor formation. Inactivation of both *RB1* alleles in the same cell results in tumorigenesis.

There are inherited and non-hereditary forms of retinoblastoma. Because both forms are seen in different clinics, Knudson developed the "two hit" hypothesis about retinoblastoma tumor development. They stated that for a cell to acquire tumor potential, two independent events must occur. Mutations at the *RB1* locus can be spontaneous or acquired. In hereditary cases, the first mutation occurs during gametogenesis, and the other can occur spontaneously (90%) or it can be inherited from parents (10%). This mutation is found in all retinal cells as well as in all other somatic and germ cells. Up to 90% of individuals with germline mutations develop retinoblastoma. The loss of a single allele in the cell is not sufficient for tumor formation, the loss of the other *RB1* allele is also required. The second mutation occurs in somatic retinal cells. In non-hereditary cases (60%), both mutations occur after gametogenesis.

Diagnosis

Patients with retinoblastoma usually present when the tumor is confined to the eyeball. Leukocoria is the most common finding (occurs in 60% of patients). Parents notice blurred eyes. Strabismus may also be seen in macular involvement or loss of central vision. Very rarely (7% of patients) glaucoma may be accompanied by red eye, hyphema or proptosis as the initial sign. Single or multiple tumor foci can be seen in one or both eyes at the time of diagnosis.

Treatment and prognosis

Each eye is treated separately according to the preservation of vision. The choice of treatment is made according to the location, size of the intraocular lesion and number of the lesion. Today, the most current treatment approach is intra-arterial administration of melphalan and topotecan. This treatment is both very effective and avoids the side effects of systemic chemotherapy. Exact indications of enucleation; vision loss, neovascular

glaucoma, detection of tumor growth towards the optic nerve in eye examination. Cryotherapy and intravitreal chemotherapy applications are other options that can be used in local tumor control. Chemotherapy is given to those with metastatic disease. Children with disease confined to the retina (whether unilateral or bilateral) have a very good prognosis, with a 5-year survival rate of more than 90%. Mortality is directly related to optic nerve involvement, extension of the tumor to the orbit, and massive choroidal involvement. In the case of disease with optic nerve involvement besides lamina cribrosa, although long-term survival is achieved with intensive chemotherapy and autologous BIT, 5-year survival is only 40%.

In retinoblastoma, it is possible to save life with early diagnosis, as well as to preserve vision to a great extent, so it is important for families to see white pupils when photographed, and eye examinations by primary care practitioners, family physicians and pediatricians during infancy.

Patients with a germline mutation (inherited form) have a significantly higher risk of developing a second tumor. Osteosarcoma is seen in 40% of such tumors.

Wilms tumor

Childhood Cancer Types

Renal tumors make up 5% of pediatric tumors. According to IARC data in 2018, 14,871 kidney tumor cases were seen in the world. The frequency is similar in boys and girls. It is most common at the age of 3-4 years. 75% of cases are between the ages of 1-5. Nephroblastoma (Wilms tumor) is the most common renal tumor in children, and less common are clear cell sarcoma of the kidney, malignant rhabdoid tumor, and renal cell carcinoma. It is a benign, congenital mesoblastic nephroma seen in newborns up to 3 months of age.

Etiology and risk factors

They are embryonic tumors of known genetic etiology. It is known that the disease occurs with the deletion of the tumor suppressor gene on chromosome 11. WAGR syndrome, genitourinary anomalies, pseudohermaphroditism, Drash syndrome, congenital aniridia (11p13 deletion), congenital hemihypertrophy are known associated anomalies. It is usually

sporadic.
1% is familial.

Symptoms and findings

Abdominal swelling and detection of a mass in the abdomen (by the mother or the doctor) are noticed. Its systemic symptoms are not as pronounced as neuroblastoma. Although hematuria and hypertension are not common, they support the diagnosis. Neuroblastoma, other benign and malignant causes of abdominal mass should be considered in the differential diagnosis.

Diagnosis

In addition to standard blood tests, the status of the primary tumor and the presence of metastases are investigated by ultrasonography and abdominal/thoracic tomography. Urinalysis and blood pressure should not be forgotten. If an early stage and kidney tumor is considered following the clinical radiological evaluation, nephrectomy and tumor resection are performed for diagnostic and therapeutic purposes. Wilms tumor staging is used for staging. It is called stage 1,2,3,4 and if there is bilateral kidney involvement, stage 5. Liver, bone, lung metastases are carefully examined. In the presence of hemihypertrophy, aniridia, and Beckwith Wiedeman syndrome, infants are followed closely for Wilms tumor development, with examination every 3 months and USG every 6 months until the age of 6 years.

Treatment and prognosis

If an early stage and kidney tumor is considered following the clinical radiological evaluation, nephrectomy and tumor resection are performed for diagnostic and therapeutic purposes. If surgery is risky in large tumors, the tumor is reduced with preoperative chemotherapy with chemotherapy for 4-12 weeks and then surgery is performed. Nephrectomy and tumor resection are performed in surgery. Radiotherapy is also used in advanced stage and metastatic diseases. Stage, presence of anaplasia, blastemal subtypes are high-risk groups. In the treatment, standard, intermediate and high risk groupings are made and treatment preferences are made accordingly. Treatment success is 90%-100% in the early stages, and around 90% even in the advanced stages. In this respect, it is extremely important to send these patients to experienced centers as soon as possible.

Primary Liver tumors

Childhood Cancer Types

Liver tumors are rare in childhood. hepatoblastoma accounts for 80%, hepatocellular carcinoma 15-20%, other rare liver tumors less than 5% (rhabdoid tumor, sarcomas, benign tumors). Liver tumors constitute 1.7% of all childhood cancers, both in the IARC series reflecting the whole world, and in the data of the Ministry of Health and TPOG/TPHD from Turkey. In 2018, 4578 cases were reported in the world. Hepatoblastoma is more common in infants and toddlers, and hepatocellular carcinoma is more common in school-age children and adolescents.

Etiology and risk factors

The cause of hepatoblastoma is unknown. Associations with fetal alcohol syndrome, hemihypertrophy, Beckwith-Wiedeman syndrome, Li-Fraumeni syndrome, glycogen storage diseases, familial adenomatous polyp, trisomy 18 are known. Hepatocellular carcinoma is also associated with glycogen storage diseases, familial adenomatous polyp, hereditary tyrosinemia, neurofibromatosis, ataxia telangiectasia, Fanconi anemia, hepatitis B and C, and congenital liver diseases.

Symptoms and findings

Hepatoblastomas usually present with an asymptomatic mass in the right upper quadrant of the abdomen. Sometimes there is also malaise, fever, pain, lack of appetite and weight loss. Symptoms of associated diseases are also seen. While, hepatocellular carcinomas, on the other hand, present with a mass in the right upper quadrant, systemic signs and symptoms are more pronounced. Abdominal distension, ascites, and signs and symptoms depending on the prevalence in advanced stages are seen.

Diagnosis

Liver tumors should be kept in mind in cases presenting with abdominal swelling and a mass in the right upper quadrant. Attention is paid to co-morbid diseases and signs and symptoms depending on the prevalence of the disease.

Complete blood count, biochemistry analysis, AFP measurement, hepatitis markers, USG, CT and MRI examinations are planned according to location. Diagnosis is made by biopsy.

In staging, SIOP PRE-TEXT staging is used, which takes into account the involvement of liver sectors and lobes, vascular involvement, and the presence of adjacent and distant metastases. In particular, the presence of lung metastases should also be investigated. In the differential diagnosis, non-tumor causes that enlarge the liver, other benign and malignant tumors of the liver should be considered.

Treatment and prognosis

In cases with clinical radiological suspicion, primary surgical resection can be performed in cases diagnosed with tru-cut biopsy in cases diagnosed very early, but since most cases present with large or widespread disease, the tumor should be reduced with chemotherapy before surgery and then surgery should be planned. Liver transplantation is used in non-metastatic diseases where resection is not possible. In chemotherapy, according to stage and risk groups, the SIOP group uses PLADO-based protocols, while the COG group adds 5-FU in high-risk cases. The general survival rate is 60-70% in hepatoblastomas and 25-20% in hepatocellular carcinomas.

Bone tumors

According to the 2018 data of the World Health Organization (WHO) International Agency for Research on Cancer (IARC), 11597 cases of bone tumors were reported in the world in 2018, accounting for 4.18% of all pediatric cancer cases. 650-700 children are newly diagnosed each year in the United States. According to the 2009-2019 data of the Turkish Pediatric Oncology Group (TPOG) and the Turkish Pediatric Hematology Association (TPHD), it constitutes 6,8% of all childhood cancers in our country, and 5,3% according to the 2016 data of the Ministry of Health.

Osteosarcoma

Childhood Cancer Types

Osteosarcoma accounts for 60% of cases and is mostly seen in adolescents and young adults. Metaphyses of long bones are more affected. Distal femur involvement was noted in

more than 40% of cases, with a decreasing frequency of proximal tibia, proximal humerus, middle and proximal femur involvement. It is more common among men.

Etiology and risk factors

Simultaneous monitoring of the growth burst and peak time in adolescents is explained by rapid bone growth and malignant transformation. It is more common in those who have received radiotherapy and is also more common in those who have received alkylating chemotherapeutic. Paget's disease, fibrous dysplasia, and chronic osteomyelitis also increase the risk of osteosarcoma. In addition, studies have found an underlying genetic mutation in 18% of patients with osteosarcoma. Most of these are detected in the RB1 gene (associated with retinoblastoma) or the TP53 (associated with Li Fraumeni syndrome) gene.

Symptoms and findings

Patients present with pain accompanied or not accompanied by a soft tissue mass in the affected area. Symptoms often begin a few months earlier. Systemic symptoms (fever, weight loss) are rare. There may be elevated ALP and LDH levels in the laboratory.

Diagnosis

Radiologically, instead of the normal trabecular bone structure, bone destruction with unclear borders and spreading around is seen. In addition to this situation, the Codman triangle appearance can be observed with periosteal new bone formation and elevation of the bone cortex. Calcification foci in the soft tissue with the appearance of "radial or sunburst" are often accompanied. The most common sites of metastasis are the lungs (≤20% of newly diagnosed patients) and other bones (10%). Thoracic CT and bone scan are essential for screening for metastatic disease. PET-CT can be used to evaluate treatment response. Tissue sampling is required to make a diagnosis other than the characteristic finding on radiological images. The selection of the biopsy site is critical, the surgeon who will perform the final surgical operation must perform the biopsy.

Treatment and prognosis

Chemotherapy is usually starts before surgery (neoadjuvant chemotherapy). In this way, it is aimed to control micrometastatic disease and shrink the tumor. A detailed evaluation of the histological response to chemotherapy is also provided with pre-surgical

chemotherapy. Poor histological response (>10% viable tumor tissue) is a poor prognostic factor. Drugs shown to be effective in osteosarcoma; doxorubicin, cisplatin, high-dose methotrexate, ifosfamide and etoposide. Histological response to neoadjuvant chemotherapy is the best predictor of clinical course. In localized disease involving 90% or more tumor necrosis, a long-term disease-free survival of 70-75% is expected. Other favorable prognostic factors are distal skeletal lesions, long duration of symptoms, age over 20, female gender, tumor DNA index close to diploid. Presence of metastatic disease or multifocal bone lesions at diagnosis are poor prognostic factors.

Ewing Sarcoma

Childhood Cancer Types

Ewing sarcoma is the second most common bone-derived malignant tumor, it can be seen at any age from play-age child to young adult. It is more common in men.

Ewing sarcoma accounts for only 30% of primary bone tumors, with fewer than 200 new cases occurring each year in the United States. Although it is usually seen as a tumor of the bone, it can also originate primarily from soft tissue. (Extraosseous Ewing sarcoma or peripheral neuroectodermal tumor-PNET).

Etiology and risk factors

Mutations in the TP53 gene, RET gene, or PMS2 gene have been demonstrated in a small group of patients with Ewing's sarcoma. It is also stated that Ewing sarcoma is more common in children with hernia (especially umbilical hernia), but the reason for this is unknown.

Symptoms and findings

Pain in the affected area with or without soft tissue swelling or redness is the general symptom of presentation. Symptoms often begin a few months earlier. Tumor-related fever and weight loss may occur.

Diagnosis

The radiological appearance of Ewing's sarcoma is confused with osteosarcoma, although it is seen in the diaphysis of the long bones. Metastatic disease is found in 25% of patients at diagnosis. Lung (38%), bone (especially vertebrae) (31%) and bone marrow (11%) are the most common sites of metastasis. Thoracic CT, bone scan and bilateral bone marrow aspiration and biopsy are required for staging. PET-CT can be used to evaluate response to treatment. A biopsy should be done to make the diagnosis. The presence of t(11;22) cytogenetically is compatible with Ewing sarcoma and PNET and is observed in 85-90% of tumors. These tumors express the *c-myc* protooncogene.

Treatment and prognosis

Treatment usually begins with chemotherapy after the biopsy. Local control can be achieved with surgery, radiotherapy, or both. Combined therapies using dactinomycin, vincristine, doxorubucin, cyclophosphamide, etoposide and ifosfamide are used in the treatment of Ewing's sarcoma. Long-term disease-free survival rate of 70-75% is expected in patients with small localized primary tumors. Survival expectancy in metastatic disease is poor. Autologous hematopoietic stem cell transplantation can be used as part of treatment in high-risk disease.

Soft tissue Tumors

According to the 2018 data of the World Health Organization (WHO) International Agency for Research on Cancer (IARC), 17327 soft tissue sarcoma cases were reported in the world in 2018, accounting for 9.1% of all pediatric cancer cases. According to the 2009-2019 data of the Turkish Pediatric Oncology Group (TPOG) and the Turkish Pediatric Hematology Association (TPHD), it constitutes 6,9% of all childhood cancers in our country, and 6,1% according to the 2016 data of the Ministry of Health. The most common soft tissue sarcoma is rhabdomyosarcoma, other soft tissue sarcomas include synovial sarcoma, fibrosarcoma, and malignant fibrous histiocytoma.

Rhabdomyosarcoma

Childhood Cancer Types

Rhabdomyosarcoma is the most common soft tissue sarcoma of childhood and constitutes 10% of solid tumors in children. The most common age range is between 2-5 years. In 70% of patients, the diagnosis is made before the age of 10. The second most common age group is adolescence, and tumors are seen in the extremities. It is seen more in boys than girls.

Etiology and risk factors

Although the pathogenesis of rhabdomyosarcoma is unknown, there are rare cases with genetic predisposition. The risk of being seen increases in Li-Fraumeni syndrome. Two characteristic chromosomal translocations [t(2;13) and t(1;13)] have been described in alveolar rhabdomyosarcoma. t(1;13) is an indicator of good prognosis in metastatic alveolar rhabdomyosarcoma, whereas a worse outcome is expected with t(2;13).

Symptoms and findings

Initial signs and symptoms of rhabdomyosarcoma vary according to the location of the tumor. For example, a patient with orbital rhabdomyosarcoma may present with proptosis, while a patient with bladder rhabdomyosarcoma may present with hematuria, pelvic mass, and globe associated with urinary system compression.

Diagnosis

Plain radiography and CT and/or MRI should be used to demonstrate the extent of the primary tumor and local lymph node involvement. Thoracic CT should be performed to show the presence of pulmonary metastases in the lungs where metastases are most common. A bone scan is done to show bone metastases. Bilateral bone marrow biopsy and aspiration are used to exclude bone marrow involvement. In special cases, other tests can be done. For example, CNS involvement can be evaluated with lumbar puncture in parameningeal primary tumors.

Rhabdomyosarcoma can occur anywhere in the body.

Rhabdomyosarcoma is subdivided according to pathological features, it is a subgroup of embryonal (60-80%), botroid type embryonal rhabdomyosarcoma, alveolar (~15-20%), undifferentiated sarcoma (8%), pleomorphic (1%) seen in adults, and others (11%). All of these subtypes have specific areas of involvement and have different metastatic potentials and clinical courses.

Treatment and prognosis

Optimal management and treatment of rhabdomyosarcoma is complex and requires the use of combined treatment modalities. The tumor should also be removed when appropriate, but this is often not possible due to the location and region of origin of the tumor. Radiotherapy is used for the control of local tumor both microscopic and gross disease remnant. It is applied in all patients except localized completely removed tumor. Chemotherapy is used for all rhabdomyosarcomas, including those that were completely removed at the time of diagnosis. Staging is done by primary tumor localization, group, tumor lymph node metastasis classification and which regimen will be given for how long is determined. Vincristine, dactinomycin and cyclophosphamide have been shown to be the most effective drugs in the treatment of rhabdomyosarcoma. Factors affecting long-term disease-free survival from the moment of diagnosis; age of the patient, extent of tumor at diagnosis, location of primary tumor, pathological subtype, response to treatment. While children with localized disease at the time of diagnosis have a three-year disease-free survival rate of 70-75%, those with metastatic disease are worse off (39% disease-free three-year survival).

Germ cell tumors

According to the 2018 data of the World Health Organization (WHO) International Agency for Research on Cancer (IARC), 10230 germ cell tumor cases were reported in the world in 2018, accounting for 5,3% of all pediatric cancer cases. According to the 2009-2019 data of the Turkish Pediatric Oncology Group (TPOG) and the Turkish Pediatric Hematology Association (TPHD), it constitutes 6.6% of all childhood cancers in our country, and 2.1% according to the 2016 data of the Ministry of Health.

Childhood Cancer Types

Most malignant gonadal tumors in children are germ cell tumors. Sacrococcygeal tumors are most common in girls under the age of 1. Testicular germ cell tumors are most common under 4 years of age and after puberty. The risk of testicular cancer increases in the presence of an undescended testis.

Etiology and risk factors

Germ cell tumors develop from primordial germ cells and may contain benign and malignant parts in different regions. Germ cell tumors histologically consist of different types such as teratoma, endodermal sinus tumor, embryonal carcinoma.

Symptoms and findings

The clinic of germ cell tumors depends on the location. Extragonadal germ cell tumors can be located in the midline, in the suprasellar and pineal regions of the brain, in the midline in the mediastinum, and in the retroperitoneal and sacrococcygeal regions of the abdomen. AFP is increased in endodermal sinus tumors, AFP is found to be higher than normal in the first 8 months of life, so its amount should be evaluated according to age. β-HCG is increased in choriocarcinoma and germinoma.

Diagnosis

Since germ cell tumors are chemosensitive and radiosensitive, biopsy is sufficient for diagnosis in intracranial germ cell tumors, and total resection is recommended in other regions, if possible. Diagnosis is made by pathology results and AFP, B-HCG values.

Treatment and prognosis

Intracranial germ cell tumors are treated with regimens containing ifosfamide, platinum, etoposide. They respond very well to chemotherapy and radiotherapy, chemotherapy and radiotherapy are used after surgical resection in other regions, bleomycin, etoposide and platinum are the most preferred agents. Cure rates are over 90%. The prognosis is worse in cases where total excision is not possible.

Other tumors

Among the subgroups of childhood cancers that are already rare, there are also tumors that are much rarer in children. Tumors such as adrenocortical carcinoma, thyroid carcinoma, nasopharyngeal carcinoma, malignant melanoma, skin cancers, rare carcinomas, pulmonary blastoma can be given as examples of rare tumors of childhood.

RESOURCES

1. Philip A. Pizzo MD, David G. Poplack MD, Principles and Practice of Pediatric Oncology, ed 7, Wolters Kluwer, 2016
2. Nathan DG, Orkin SH, Ginsburg D, et al, editors: nathan and Oski's hematology of infancy and childhood, ed 6, Philadelphia, 2003, Saunders.
3. Robert M. Kliegman & Joseph St. Geme , Nelson Textbook of Pediatrics, International Edition, ed 21, Elsevier, 2019
4. Buhtoiarov IN. Pediatric Lymphoma Pediatrics in Review 2017; 38(9):410-423.
5. Kara F, Keskinkılıç B (Eds) Türkiye Kanser İstatistikleri, 2017. Ministry of Health, 2019
6. Atun R, Bhakta N, Avram Denburg A, et al. The Lancet Oncology Commission Sustainable care for children with cancer: a Lancet Oncology Commission Lancet Oncol 2020 21: e185-e224,2020
7. Steliarova-Foucher E, Colombet M, Ries LAG, et al. International incidence of childhood cancer, 2001–10: a population-based registry study. Lancet Oncol 2017; 18(6): Published Online April 11, 2017 http://dx.doi.org/10.1016/ S1470-2045(17)30186-9
8. Kutluk MT, Yeşilipek A. Pediatric cancer registry in Turkey 2009-2019 (TPOG & TPHD). ASCO 2020 Annual meeting. J Clin Oncol 38: 2020 (suppl; abstr e22513) DOI: 10.1200/JCO.2020.38.15_suppl.e22513

SECTION 3

Primary Protection

3.1. GENERAL INFORMATION

Cancer and cancer-related health problems are an important public health problem in our country as well as all over the world. Life years lost due to premature deaths, decreased productivity, the economic burden of disease and treatment-related costs, and the long-term effects of cancer and its treatment on the quality of life of survivors lead to negative effects in the community. The impact of cancer on public health will continue to increase with each passing day as the life expectancy of individuals in societies increases and the incidence of some cancer types increases accordingly.

Cancer is a heterogeneous group of diseases that differ in location, morphology, molecular features, clinical behavior and response to treatment in humans and cause abnormal cell growth. It is classified as benign and malignant (benign and malignant). Benign cancers can be defined as local tissue growths with predominantly normal features. Many cause mild symptoms and are amenable to surgical treatment. When they occur in organs that cause compression-related findings such as brain tumors and where surgery cannot be performed easily, or when they secrete hormones or other substances (such as pheochromocytoma), they can be fatal due to their systemic effects. Malignant neoplasms are characterized by structural and functional changes relative to normal tissue and progressive growth of abnormal cells. Characteristic of malignant tumors is their ability to invade surrounding tissue and migrate and multiply to other organs via blood and/or lymph.

Cancers show differences at the molecular level according to phenotypic (receptor, gene presence) and genetic changes (gene mutation, etc.). In recent years, great progress has been made in the understanding of the molecular and cellular mechanisms of carcinogenesis.

Studies on cancers in the long term justify the importance of developing screening approaches and applications for the early detection of cancers that have not yet clinically detected in healthy individuals. The evolution of cancer epidemiology has provided the basis for the identification of cancer determinants and knowledge of possible causes and possible preventive strategies. Epidemiological studies and the examination of environmental and genetic factors in the development of cancer are of great importance in the fight against cancer. Analytical studies have shown the causal role of specific exposures in the etiology of some malignant neoplasms [1].

3.2. ETIOLOGIC RISK FACTORS OF CANCER

3.2.1. Tobacco Use

Tobacco is one of the major causes of human cancers worldwide [2].

Tobacco-related cancers include cancers of the lung, nasal cavity, larynx, oral cavity, pharynx, esophagus, stomach, liver, pancreas, colorectal, ovary, uterus, cervix, kidney, and bladder, and myeloid leukemia.

It has been reported by the IARC Monograph Program that there are over 70 carcinogenic substances in tobacco smoke and 16 of them cause cancer in humans (Group 1) [3].

3.2.2. Diet and Obesity

Although significant research has been conducted in recent years, the precise role of the nutritional factor in causing or protecting against cancer in humans is largely unclear. However, there is sufficient evidence that the risk of liver cancer increases with aflatoxin exposure. A meta-analysis on nutrition and cancer concluded that high consumption of red meat in addition to processed meat is associated with an increased risk of colorectal cancer [4].

There is also evidence that weight gain is associated with an increased risk of cancer of the esophagus (adenocarcinoma), pancreas, colorectum, postmenopausal breast cancer, endometrium, and kidney [5].

3.2.3 Alcohol Use

Sufficient evidence is considered by the IARC to identify drinking alcohol as a group 1 carcinogen. High levels of alcohol use increase the risk of cancer of the oral cavity, pharynx, larynx, esophagus, liver, pancreas, colorectum, and female breast cancer [6].

3.2.4. Infectious Factors

Infectious agents are considered to be the second most important factor in cancer risk in the world. Nine infectious agents were classified as group 1 carcinogens (8.1 percent). 6 of them were associated with certain types of human cancer: Epstein–Barr Virus (EBV) for nasopharyngeal cancer, Hodgkin Lymphoma and Non-Hodgkin Lymphoma, Human Papilloma Virus (HPV) for anogenital cancer, mouth and oropharyngeal cancers, Hepatitis

B Virus (HBV) and Hepatitis C Virus (HCV) for liver cancer, Human Immunodeficiency Virus Type 1 (HIV-1) Non-Hodgkin Lymphoma and Human T- Lymphotropic Virus Type 1 (HTLV-1) Non-Hodgkin Lymphoma, Helicobacter Pylori for gastric cancer , Schistosoma Haematobium parasite poses a risk for bladder cancer and Opisthorchis viverrini for liver cancer [7].

3.2.5. Vocational Risks and Air Pollution

Exposure to carcinogens such as asbestos, arsenic, and silica is still common today. Estimates of the global cancer burden attributed to occupation in high-income countries are 2-3 percent [8].

3.2.6. Ionizing and Non-ionizing Radiation

The share of ionizing radiation in cancer causes in high-income countries is 3-5% [8]. Acute lymphocytic leukemia, acute and chronic myeloid leukemia, and breast, lung, bone, brain and thyroid cancers may occur due to such radiation exposure [9].

3.2.7. Global Cancer Burden

Around the world, 18 million 78 thousand people were diagnosed with new cancer in 2018. In the same year, approximately 9 million 550 thousand deaths due to cancer occurred (5 million 385 thousand men and 4 million 169 women). The most common cancers in men were listed as lung, prostate, colorectal, stomach, and liver cancers, while in women, this order was breast, colorectal, lung, cervix, and thyroid cancers [10]. The distribution of newly diagnosed cancer types in men and women worldwide in 2018 is shown in Figure 1 [11].

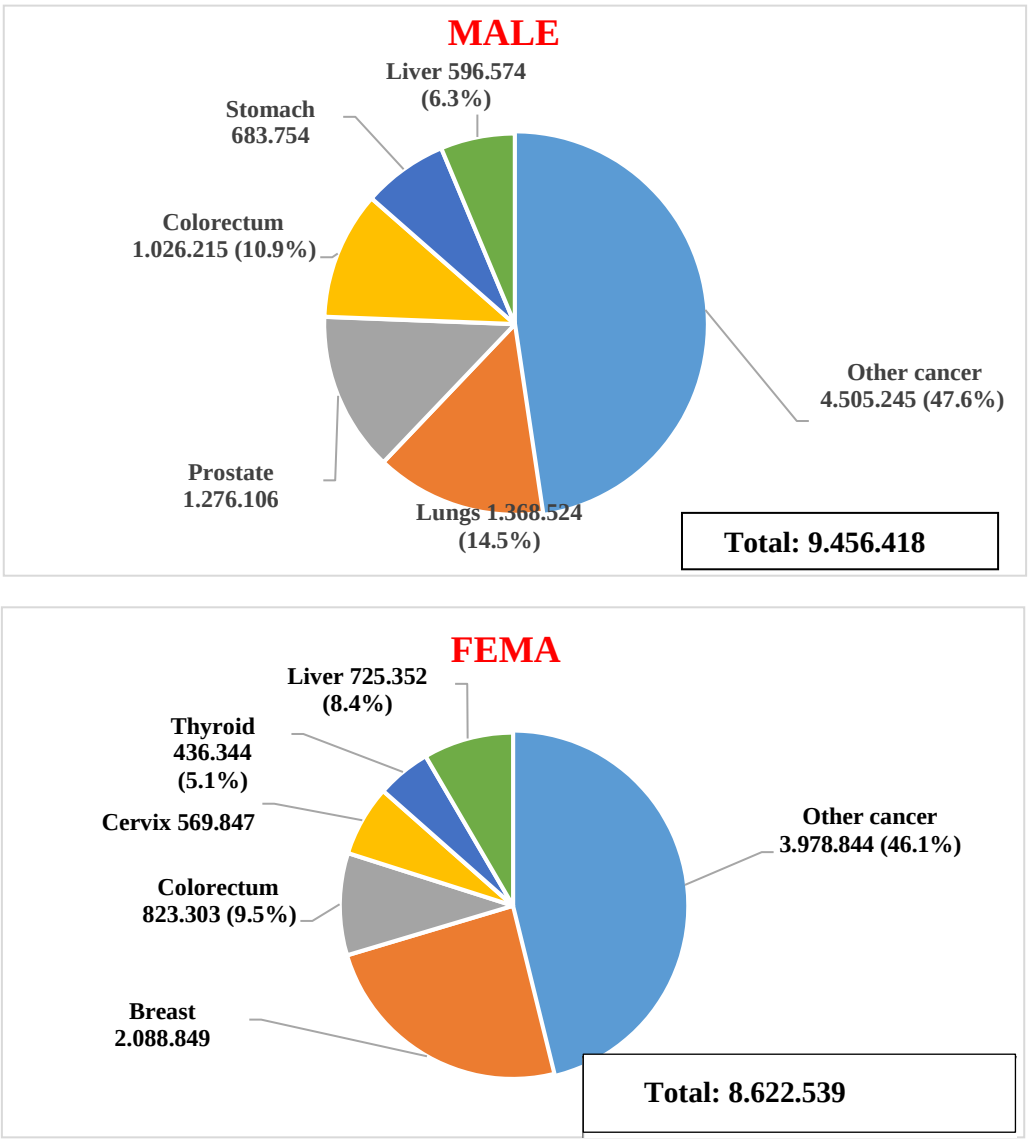


Figure 1. Number of Case of Newly Diagnosed Cancer Types in Males and Females Worldwide in 2018 (All Age Groups)

3.2.8. Primary and Secondary

Protection Primary Protection

Many determinants involved in the formation of malignant neoplasms (UV radiation, ionizing radiation, tobacco and alcohol consumption, obesity, some viruses and parasites, exposure to some chemicals, etc.) are well defined for primary protection, that is, prevention of the disease before it occurs. As many studies have shown, it is possible to reduce the incidence of cancers to a great extent by reducing or even eliminating exposure to certain agents.

Today, cancer prevention strategies have turned into an individual-focused model with public health interventions instead of an intense environmental and lifestyle approach, and the fight against cancer has gained greater power with advances in prevention, early diagnosis and treatment.

Secondary Protection

Considering that the prevention of many cancers with primary prevention is still limited and based on the fact that the detection of prognosis of many cancers is that good, early diagnosis methods offer us an important option. Of course, this is only the case when there is an effective treatment for the disease and the clinic of the cancer is present.

In order for a screening program to be implemented, a number of conditions must be met. First of all, there should be a screening test that will accurately identify sick and healthy individuals. In other words, both sensitivity and specificity should be high, approaching 100 percent. While high sensitivity is important, given that the aim of screening is to collect, if possible, all detectable preclinical cancer cases in the population, specificity plays a dominant role. In other words, for each case that turns out to be a true cancer in the diagnostic study (assuming 100 percent sensitivity), there will be 5-50 cases that are incorrectly identified and ultimately found to be non-cancerous. This is proving to be unacceptable due to the very high psychological and economic costs. Increasing the specificity (in which case the sensitivity decreases) by developing better test or test combinations or by changing the positivity criterion of a particular test may be a solution in these cases. In addition, relatively high prevalence cancers ("high-risk" groups) can be selected to increase the number of true positives. Regardless of which screening programs are applied to which groups, it is also necessary for the test to be safe, easy and fast to be administered and to be widely accepted by the society for the screening program. Another requirement is that the cancer screening test should be affordable. However, different ways of preventing a cancer case or death, inexpensive or not, should be better evaluated with cost-effectiveness analyzes [12].

Conclusion

Cancers are a diverse group of diseases with complex distributions and different etiological causes. The development of information and control strategies about the causes of cancers has led to the preparation of lists such as the "European Code Against Cancer" recommendation list [13] for their prevention.

European Code Against Cancer

12 ways to reduce your cancer risk:

1. Do not smoke. Do not use any tobacco product.
2. Do not smoke in your home. Support tobacco-free workplace policies.
3. Take action to be at a healthy body weight.
4. Be physically active in your daily life. Limit the time you spend sitting.
5. Eat healthy:
    - Consume plenty of grains, legumes, vegetables and fruits.
    - Limit high-calorie foods (high sugar and fatty foods), avoid sugary drinks.
    - Stay away from processed meat products, consume limited red meat, stay away from very salty foods.
6. If you drink alcohol, limit your use. You should not drink alcohol to prevent cancer.
7. Especially keep children away from excessive sun. Wear sun screen. Do not use a solarium.
8. Protect yourself from cancer-causing substances by following the health and safety rules in the workplace.
9. Make sure you are not exposed to radiation from high radon levels in your home. Take measures to reduce high radon levels.
10. For women:
    - Breastfeeding reduces the mother's cancer risk. Breastfeed your baby.
    - Hormone treatments increase the risk of cancer. Limit hormone use.
11. Have your children vaccinated:

- Hepatitis B vaccine (in newborns).
- Human papillomavirus vaccine (HPV) (in girls).

12. Get your screenings under the National Cancer Screening Programs:
    - Bowel cancer (men and women)
    - Breast cancer (in women)
    - Cervical cancer (in women).

With comprehensive policies to be developed for cancer control, most of the cancers can be prevented. The greatest benefit is that it is the most cost-effective intervention to prevent lung cancer in countries where tobacco control programs are implemented.

Cancers will be among the leading causes of death for human beings in the next century. Significant efforts are being made in the public and private spheres to develop effective therapeutic approaches. Prevention of known causes of cancer, especially in countries with limited resources, it remains to be the most important approach in reducing the consequences of cancer. Control of tobacco and smokeless tobacco products, limiting alcohol intake, reducing overweight and obesity, increasing physical activity, preventing exposure to harmful rays of the sun, control of occupational carcinogens and vaccination against carcinogenic infectious agents are the basic approaches in the fight against cancer.

3.3. COUNTRY EXAMPLES IN CANCER SCREENING

USA: No cancer screening is offered for free at the national level. National Cancer Institute recommends:

1. PAP smear test (Once in 2 years between the ages of 21-65)
2. Stool occult blood test (1 per year aged 50 and over)
3. Colonoscopy (1 in 10 years between the ages of 50-75)
4. Mammography (1 per year for 40-74 years old)

The Medicaid program for low-income people generally covers all cancer screenings free of charge.

Canada also offers screening tests at the national level free of charge.

1. PAP smear test (1 in 3 years between the ages of 25-69)
2. Stool occult blood test (1 in 2 years between 50-74 years old)

3. Mammography (1 in 2 or 3 years, 50-74 years old)

Currently, Australia operates nationally coordinated screening programmes.

1. Mammography for breast cancer screening (50-74 years, with an invitation letter once every 2 years. 40-49 and over 74 years old are free of charge, but letters are not sent).
2. PAP smear (1 in 2 years between the ages of 18-70)
3. Stool occult blood test (1 in 2 years between the ages of 50-74)

In **New Zealand**, the National Screening Unit (NSU) is responsible for the nationally run screening programme;

1. Breast cancer
2. Cervical cancer
3. Antenatal HIV

United Kingdom: The national screening program is considered by many experts in the field to be the best screening system as it manages all aspects of screening policy and implementation. Programs run in the UK;

1. breast cancer; every 3 years for women aged 50-70
2. Cervical cancer screening:
    a. Every 3 years for women aged 25 to 49 and
    b. Every 5 years for women aged 49-64 in all UK states
3. Colorectal cancer screening every 2 years aged 60-74 years

In Spain, the NHS (National Health System) organization is decentralized. For this reason, programs are carried out distributed to the regional health systems of 17 autonomous regions.

Breast cancer screening is the oldest program. For colorectal cancer, a highly effective screening program was implemented in 2015. The cervical cancer screening program is currently in place, aiming to reduce inequalities in screening access by sending invitations to women who have not been tested in the past 3 years.

European Union

The European Union has been recommending population-based breast, cervical and colorectal cancer screening since 2003 and has been determining the basic criteria for the realization of policies. Since then, all EU countries have implemented screening programs, albeit with different implementation models.

Breast cancer (45-49 years old once in 2 or 3 years, 50-69 once in 2 years, 70-74 1 in 3 years)

- All EU countries except Bulgaria, Croatia and the Slovak Republic have a national breast cancer screening policy mandated by law or official recommendation.
- While the Breast Cancer Screening program is not supported by the public in Luxembourg, it is carried out with partial public support in Portugal. In all the remaining EU countries, the breast cancer screening program is publicly funded.

Cervical Cancer (varying from country to country, at intervals of 3-5 years)

- All Member States except Bulgaria, Cyprus and Luxembourg have a national cervical cancer screening policy, which is mandated by law or official recommendation.
- All other countries have publicly funded population-based screening programs where screening tests are conducted free of charge.

Colorectal Cancer (Once in 2 years aged 50-74 years)

- All EU countries except Bulgaria, Romania and the Slovak Republic have a colorectal cancer screening policy or an official recommendation mandated by law.
- The program is publicly funded and tests are provided free of charge to all except Croatia, where costs are reimbursed through health insurance.

In Egypt, only mammography is carried out as a national screening program.

There is no cancer screening program routinely implemented at the national level **in China**. However, the program, which started in 2009, screened 100 million women for cervical cancer and screened more than 30 million women for breast cancer, is planned to be expanded to cover 80% of all women by 2022.

The Indian government, on the other hand, implemented the country's first screening program for breast and cervical cancer in 2016, covering women over the age of 30 living in 100 different regions.

RESOURCES

1. Lagiou, P., Trichopoulos, D., and Adami, H.O. (2008). Concepts in cancer epidemiology and etiology. In H.O. Adami, D. Hunter, and D. Trichopoulos (eds.) Textbook of Cancer Epidemiology, pp.
2. International Agency for Research on Cancer (2004). IARC Monographs on the Evaluation of the Carcinogenic Risks to Humans. Volume 83. Tobacco Smoke and Involuntary Smoking. Lyon: International Agency for Research on Cancer.
3. https://monographs.iarc.fr/wp-content/uploads/2018/06/mono100E-6.pdf
4. Chan, D. S., Lau, R., Aune, D., Vieira, R., Greenwood, D. C., Kampman, E., & Norat, T. (2011). Red and processed meat and colorectal cancer incidence: meta-analysis of prospective studies. PloS one, 6(6), e20456. https://doi.org/10.1371/journal.pone.0020456
5. World Cancer Research Fund and American Institute for Cancer Research (2007). Food, Nutrition, Physical Activity and the Prevention of Cancer: A Global Perspective. Washington, DC: AICR.
6. Baan, R., Straif, K., Grosse, Y., et al. (2007). Carcinogenicity of alcoholic beverages. The Lancet Oncology, 8, 292–3.
7. Parkin, D.M. (2006). The global health burden of infection-associated cancers in the year 2002. International Journal of Cancer, 118, 3030–44.
8. Doll, R. and Peto, R. (2005). Epidemiology of cancer. In D.A. Warell, T.M. Cox, and J.D. Firth (eds.) Oxford Textbook of Medicine (4th ed.), pp. 193–218. Oxford: Oxford University Press.
9. International Agency for Research on Cancer (2000). IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Volume 75. Ionizing Radiation, Part 1: X-radiation and Gamma-radiation, and Neutrons.
10. GLOBOCAN 2018; https://gco.iarc.fr/today/home.
11. https://gco.iarc.fr/today/data/factsheets/populations/900-world-fact-sheets.pdf
12. Oxford Texbook of Global Public Health, 2015, Cancer Epidemiology, 923.
13. https://www.europeancancerleagues.org/wp-content/uploads/ecac_turkish.pdf

3.4. PROTECTION STRATEGIES

Kanser, son yıllarda tüm dünyada olduğu gibi Türkiye'de de en önemli toplumsal sağlık problemlerinden biridir. It is predicted that cancer, which is the second leading cause of death in the world, will increase rapidly until 2030 and take the first place [1].

3.4.1. Primary Prevention

Cancer Risk Factors

Cancer, like other non-communicable diseases, is a group of diseases in which many factors are among the causes of its formation. Among these reasons, there are 5-10% genetic and 90-95% environmental factors. The most important of these factors (excluding tobacco and tobacco products) is the lifestyle that causes obesity, which consists of diet-weight-physical activity components. Many studies have found that obesity is associated with cancer of the esophagus, colon, kidney, thyroid, liver, and prostate in men, and cancer of the endometrium, esophagus, kidney, ovary, gall bladder, postmenopausal breast, pancreas, and thyroid in women. For this reason, if efforts to prevent obesity and to increase adequate and balanced nutrition and physical activity increase, the frequency of cancer will decrease with weight control [2].

Diet

A healthy diet is taking in sufficient and balanced amounts of macro and micro nutrients (carbohydrate, protein, fat, vitamin, mineral and water) necessary for the correct and regular functioning of the cells that make up our body. Insufficient or unbalanced use of these nutrients can cause many health problems.

Today, eating habits are changing rapidly. Problems with food safety and malnutrition differ from country to country and even within countries. Processed foods are becoming more accessible and replacing traditional foods and eating habits [3]. With the effect of urbanization, industrialization, working standards and globalization, traditional eating habits are also changing. With the decrease in the time to be devoted to eating, the fast food culture has come to the fore. In the report of the Food and Agriculture Organization (FAO), it is stated that there are varying levels of malnutrition, overnutrition and/or micronutrient deficiencies in all countries of the world.

Nutritional habits are involved in the formation of approximately 1/3 of all cancers [4]. While dietary habits are the most effective with 35% in cancer formation, there are studies in which nutritional additives are found to be effective at the rate of 1% [5] (Table 1).

Causes of Cancer Formation	**Rate (%)**
Mistakes in nutrition	**35**
Smoking	**30**
Infection	**10**
Occupational Diseases	**4**
Alcohol USe	**3**
Environmental Pollution	**2**
Nutritional Additives	**1**
Idiopathic	**15**

Table 1. Causes and Rates of Carcinogenicity

Under normal conditions, natural dietary components do not have cancer-initiating effects. However, as a result of some measures taken to prevent the deterioration of foods and the cooking methods of foods, some substances that can cause cancer are released. Especially in agriculture, a direct and clear relationship has not been demonstrated between pesticides used to prevent, control or reduce harmful organisms and the development of cancer. However, there are findings that the frequency of bladder and colon cancer, which is known to be related to pesticide exposure, has increased approximately 2 times, especially in agricultural workers.

Additives are substances that are generally used to keep foods intact for a long time and to extend the shelf life of processed products. Harmful microorganisms that can reproduce in foods stored in poor conditions carry a much greater risk of disease than these

substances can create. For example, additives that prevent the growth of molds and fungi actually provide a protection against cancer. If necessary precautions are taken during this period and the proliferation of fungi and mold agents is not prevented, it is not possible to eliminate the aflatoxin produced by these reproducing organisms in subsequent packaging processes. According to the International Agency for Research on Cancer (IARC), nitrates and nitrites, which are on the list of potential carcinogens, can initiate cancer when converted to nitrosamines. There is no data showing that these preservatives, which are thought to increase the risk of colon cancer in particular, increase the risk of cancer at legally permitted doses. When added to foods in legally permissible doses, these substances must remain below the nitrosamine concentration that can cause cancer in the stomach and at high temperatures. There is no evidence to suggest that coloring, flavoring and sweetening additives added to foods at legally permissible doses increase the risk of cancer. Saccharin, one of the sweeteners, has been shown to increase the risk of cancer when used in very high doses in animals. Humans do not consume these amounts of saccharin. When used in low doses and for a long time, no carcinogenic effect has been demonstrated. However, studies on the safety of long-term use in terms of cancer are not sufficient.

Food preparation and storage methods are also of great importance in terms of the formation of carcinogens in foodstuffs. The probability of occurrence of cancer-initiating substances is extremely high in foodstuffs prepared by methods of grilling, smoking, salting in wood and coal fires. Frying or preparing foods at high temperatures (above 120°C) results in the formation of heterocyclic amines. There are epidemiological studies showing that these increase some types of cancer, especially esophageal cancers. Especially the preparation of starchy foods (potato chips, etc.) at high temperatures (including frying) causes the formation of acrylamide. Acrylamide is a cancer-causing chemical, but there is no evidence yet to show that the risk of cancer increases with acrylamide formed in food in populations. However, since it is technically difficult to investigate the relationship of such foods with cancer, care should be taken regarding their consumption, especially for children.

Heterocyclic amines and polycyclic aromatic hydrocarbons are substances with high carcinogenic potential. Occurs in foods that have been cooked at high temperatures. Heterocyclic amines are formed especially in fried meat, bread, burnt, roasted vegetables, smoked, charcoal/wood-fired meat and meat products, and fish. Heterocyclic amines are important carcinogens on the IARC list. Polycyclic aromatic hydrocarbons are formed

during the smoking process of smoked (smoked) meat and fish products. In epidemiological studies, it has been shown that smoked foods increase the risk of colon and gastric cancer. Salty and pickled foods with high salt content (pickles, vine leaves, feta cheese, etc.) are especially at risk for gastric cancer. It has been shown that dietary salt increases the risk of gastric cancer, especially by potentiating the effect of Helicobacter pylori [6].

Toxins formed in foods stored in bad conditions can also cause cancer to begin. Aflatoxin produced by fungi, especially in food products that are not stored under appropriate conditions, carries a risk in terms of liver cancer. Although it is an important problem mostly in tropical and humid regions, in our country if they are not stored in appropriate conditions, aflatoxin-producing fungi can multiply in many foods, especially in grain products [7].

Cancers that have been proven to be related to nutrition are listed below:

Oral cavity, pharynx and esophageal cancers: Excess weight/obesity is an established risk factor for adenocarcinoma of the esophagus. It is thought that 60% of oral cavity, pharynx and esophageal cancers in developing countries are micronutrient deficiencies caused by low consumption of vegetables, fruits and animal products due to restricted diet. The roles of various micronutrients are not clear. However, riboflavin, folate, zinc and vitamin C deficiencies can all be factors. There is also consistent evidence that consuming beverages and foods at very high temperatures increases the risk of this cancer.

Gastric cancer: Besides other etiological factors, nutrition is thought to be important in the occurrence of gastric cancer. Evidence from case-control studies shows that excessive consumption of pickled foods with high salt content, meat, pickles and salt increases the risk of gastric cancer, and increasing the intake of vegetables and fruits in the diet reduces gastric cancer due to their vitamin C content.

Colorectal cancer: The incidence of colorectal cancer is 10 times higher in developed countries than in developing countries. It has been suggested that 80% of these incidence differences between countries can be explained by factors related to nutrition. The most well-known risk factor related to nutrition is overweight/obesity. During the cooking of meat at high temperatures, mutagenic heterocyclic amines and polycyclic aromatic hydrocarbons can be formed, and nitrites found in smoked, pickled and some processed meat products can be converted to carcinogenic N-Nitroso compounds in the large intestine. In addition, high

iron levels in the large intestine can increase the formation of mutagenic free radicals. There are studies showing a strong relationship between fat consumption per capita and colorectal cancer mortality. Possible mechanisms are that high fat intake increases the level of cytotoxic free fatty acids or secondary bile acids in the lumen of the large intestine. There are studies showing that fibrous foods increase stool volume and accelerate the passage of food through the colon, thereby diluting the intestinal contents and reducing the absorption of carcinogens by the colonic mucosa. In addition, although there are studies showing that adequate folate and calcium intake reduces the risk of colorectal cancer, more data is needed on this subject.

Liver cancer: Eating foods contaminated with mycotoxins and aflatoxins, and excessive alcohol consumption are risk factors related to nutrition.

Pancreatic cancer: Excess weight and obesity probably increase the risk of pancreatic cancer.

Breast cancer: Free estradiol probably increases the risk of breast cancer by 50% in postmenopausal women due to overweight and obesity. Another proven risk factor for breast cancer is alcohol. Depending on the amount of consumption, drinking alcohol every day causes a 7% increase in the risk of breast cancer. Although there are many studies showing that high fat intake also increases the risk of breast cancer, data on whether dietary fat alters circulating estrogen levels are limited.

Endometrial cancer: Endometrial cancer is 3 times more common in obese women than in thin women.

Kidney cancer: Overweight and obesity are established risk factors for kidney cancer and may be responsible for 30% of kidney cancers in both men and women. In Table 2, the relationship between nutrition and cancer is presented according to the level of evidence.

Table 2. Diet, Nutrition and Cancer: Levels of Evidence

Level of evidence	**Reduced risk**	**Increased risk**
Convincing	Physical activity (colorectum)	Overweight and obesity (esophagus, colon, rectum, breast, endometrium, kidney)
Probable	Vegetables and fruits (oral cavity, esophagus, stomach, colorectum*) Physical activity (breast)	Canned meat, red meat (colorectum) Salted foods and salt (stomach) Very hot drinks and foods (oral cavity, pharynx, esophagus)
Insufficient	Fiber, soy, fish, carotenoids, vitamins Micronutrients such as zinc and selenium	Animal fats, heterocyclic amines, polycyclic aromatic hydrocarbons, nitrosamines

*Many case-control studies have shown the protective effect of fruit and vegetables, while a few large studies have not supported the same effect [8].

Activities carried out in Turkey related to nutrition in the fight against cancer

- **Turkey Dietary Guidelines (TÜBER-2015):** With this nutrition guideline, information that can be understood by the public is presented with food-based approaches in providing access to energy and nutrients needed according to age, gender, physiological status and physical activity level. In the guide, with the principle of healthy nutrition based on food diversity, food groups, the amounts to be consumed daily and portion sizes are given according to age and gender, and are also defined with figures.
- **Diagnosis-Treatment-Follow-up Guide for Family Physicians in Celiac Disease**
- **National Menu Planning and Implementation Guidelines in Collective**

Nutrition Systems

- **Trainings:** Trainings are provided for healthcare professionals and the society on obesity-healthy nutrition-diabetes.
- **Arrangements made with inter-sectoral cooperation**
    - Reducing salt in bread, tomato paste, chili pepper, cheese and olives by the Ministry of Health and the Ministry of Agriculture and Forestry.
    - **Advertising regulation**: The commercial communication of foods and beverages containing foods and substances whose excessive consumption is not recommended in general nutrition diets should not be included in children's programs or in these programs.
    - **Label regulation**: Making it mandatory to write in case the nutritional elements and contents and the amount of trans fat in 100 g are above 2%.
    - **Healthy Eating Active Life Collaboration Platform:** Reducing the use of excessive salt and sugar in places where mass feeding is provided such as restaurants, kebab shops, patisseries, etc., where salt and sugar consumption have an important place.
    - **Establishment of the National Nutrition Council (UBK):** With the aim of determining policies and strategies related to health status and diseases arising directly or indirectly from nutrition and food/beverage across the country.
    - **Health Promoting Municipality (SAGEB) Cooperation Protocol**
    - **Program Collaboration Protocol for Nutrition Friendly and Supporting Physical Activity Workplace:** A protocol created with the aim of protecting and improving health by creating an environment that supports healthy living behaviors in adults.

Alcohol

Alcohol use is a potential risk factor for cancer [9]. Addressing high-risk alcohol use as a potentially modifiable risk factor for cancer is an appropriate strategy to reduce cancer burden. For example, it is estimated that 5.5% of all new cancer cases and 5.8% of all cancer deaths in the world in 2012 can be attributed to alcohol [10]. In the United States, it is estimated that
3.5% of all cancer deaths are due to alcohol consumption [11].

The risk of developing cancer increases with the amount of alcohol consumed [12].

The association between alcohol consumption and cancer risk has been extensively evaluated in epidemiological case-control and cohort studies. In a comprehensive systematic review of relevant evidence around the world, the World Cancer Research Fund/American Cancer Research Institute (AICR) report evaluated the evidence as convincing that drinking alcohol is a cause of cancers of the oral cavity, pharynx, larynx, esophagus, breast, and colorectum (in men) [13]. In addition, alcohol was judged to be a possible cause of increased risk of liver cancer and colorectal cancer (in women) [13]. The level of evidence between liver cancer and alcohol consumption was also considered convincing [14]. The International Agency for Research on Cancer (IARC), a unit of WHO, reached almost the same conclusions when it evaluated the evidence in question: Alcohol is the cause of cancers of the oral cavity, pharynx, larynx, esophagus, colorectum, liver (i.e. hepatocellular carcinoma), and breast cancer for women [15].]. For esophageal cancer, the association with alcohol use is largely squamous cell type specific.

Possible reasons why alcohol increases the risk of cancer may be related to chemicals (ethanol, acetaldehyde) that can damage the DNA of healthy cells. Alcohol can affect the breakdown of the estrogen hormone in the blood. Excess estrogen in the body is a risk factor for breast, ovarian and uterine cancers. This is of particular concern for premenopausal women and women taking menopausal hormone therapy.

Drinking alcohol impairs the processing and absorption of Vitamins A, C, D, E, Folate and Carotenoids, which are important for the body. In addition, it can lead to weight gain, which increases the risk of cancer [16]. Table 3 shows the data showing the frequency of alcohol use in our country by years.

Table 3. Frequency of Alcohol Use According to Years in the Population Aged 15 and Older

in Turkey

	Frequency of Alcohol Use (%)			
Literature Research	**Year**	**Total**	**Male**	**Female**
TurkStat-Health Statistics Yearbook	2010	12.6*	21.1	4.4.
TÜİK-Turkey Health Research	2012	10.4*	17.2	3.8.
TÜİK-Turkey Health Research	2014	14.9*	24.3	5.8
TÜİK-Turkey Health Research	2016	12.2*	19.3	5.3
Turkey Household Health Survey (Prevalence of Risk Factors of Non-Communicable Diseases, 2017)	2017	8.0**	13.1.	3.0

**Data on usage in the last 12 months.*

***Data on alcoholic beverage consumption in the last 30 days.*

According to the data of the 2011 Turkey Chronic Diseases and Risk Factors Study data: the rate of those consuming 5 or more standard drinks a day in the population over the age of 15 and evaluated in the risky alcohol use category is 1% for women, 8% for men, and 7% of the population in general. According to the Turkey Household Health Survey (Prevalence of Risk Factors for Non-Communicable Diseases) conducted in 2017, consumption of 6 or more standard drinks at least once in the last 30 days was 1.6% for women and 8.7% for men, with an average of 5.2% [17].

Activities carried out in Turkey related to alcohol in the fight against cancer arrangements made with cooperation between Sectors

1. **Legislation:** It is aimed to protect the whole society, especially our children and youth, from the harmful effects of alcohol [18].
2. "Communiqué on Warning Messages on Alcoholic Beverage Packages": Within the scope of this communiqué, it was decreed that all alcoholic beverages offered for sale in our country should include 4 health warnings [19].
3. **Within the scope of the Price and Taxation System,** tax regulation should be made for alcoholic beverages [20].

Tobacco and Tobacco Products

Tobacco use is the most important preventable cause of death [21].

Globally, 942 million men and 175 million women aged 15 and over still smoke. About three-quarters of male smokers live in countries with a medium or high human development index (HDI), while half of female smokers live in countries with a very high HDI. Although a decline in the prevalence of tobacco use has been noted in some countries, worrying trends are observed among youth and in low-income countries [22].

The prevalence of tobacco use in Turkey, which was 31.2% in 2008, decreased to 27.1% in 2012. The results of the research show that 2.2 million people stopped using tobacco products in the 4-year period between 2008 and 2012. It was determined that the prevalence of tobacco product use, which was 32.5% in 2014, showed a decreasing trend again in the Global Adult Tobacco Survey conducted in 2016 and decreased to 31.6%, and to 30.6% in the Turkey Health Survey conducted in 2016 [23].

Carcinogens in tobacco smoke were identified in the late 1950s, with evidence linking smoking with lung cancer and other cancers [24]. On the other hand, cigarette smoke material has been shown to cause tumors when stained on the skin of mice. Since then, the number of deaths attributable to tobacco smoking has increased sharply, reflecting patterns of heavy smoking in previous years [25]. On the other hand, it is now known that other tobacco products such as hookahs, pipes and cigars cause cancer in addition to cigarettes [25]. Both inhaling and smoking tobacco smoke expose users to more than 7000 toxic substances and at least 70 carcinogens, causing harm to the whole body [22].

Since pregnant smokers can give birth to babies with a higher risk of congenital disorders, cancer, lung diseases and sudden death, the harms of tobacco begin before birth. In addition, exposure to secondhand or environmental tobacco smoke is also associated with an increased risk of cancer [22].

The US Department of Public Health reported that living with a smoker increases the risk of developing lung cancer in non-smokers by 20-30% [27].

Tobacco use serves as a prototype of a disease risk factor in many ways. Smoking is the leading cause of cancer-related death and it is estimated that at least 15% of all cancers are due to smoking [28]. This rate is 25% in men and (4%) higher than in women [29]. In addition, the risk of smoking-related death increases over time as the average duration of smoking increases [30].

Today, tobacco smoking is responsible for approximately 30% of all cancer deaths in developed countries, and it is predicted that a cancer epidemic that can be attributed to tobacco smoking will occur in developing countries if the current smoking patterns continue [30].

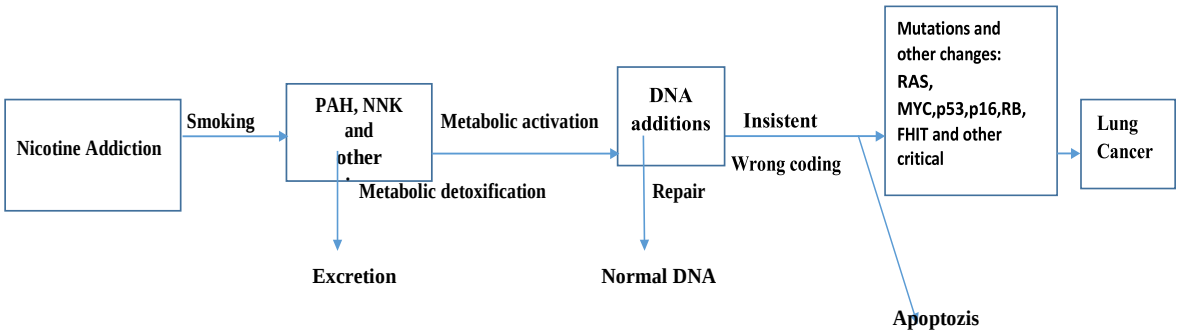
How does tobacco use cause cancer?

The carcinogens in cigarette smoke belong to several chemical classes, including polycyclic aromatic hydrocarbons (PAHs), N-nitrosamines, aromatic amines, aldehydes, volatile organic hydrocarbons, and metals. Besides these well-known carcinogens, relatively less researched ones include alkylated PAHs, oxidants, free radicals, and ethylating agents. Scientific evidence indicates that PAHs, N-nitrosamines, aromatic amines and some volatile organic agents play an important role in cancers caused by smoking. In conclusion, PAH, N-nitrosamines, aromatic amines, 1,3-butadiene, benzene, aldehydes and ethylene oxide are the most important carcinogens in terms of their carcinogenic potential and their levels in cigarette smoke [31].

On the other hand, many of these chemicals can damage DNA. Damaged DNA can cause cells to grow differently than they should, causing these different cells to turn into cancer [21].

Based on the available data, the most likely process between tobacco use and cancer development is summarized in figure 2 [32].

Figure 2. Process of Cancer Development in Tobacco Use



* PAH: Polycyclic Aromatic Hydrocarbons, NNK: Nitrosamine 4-(methylnitrosamine)-1-(3 pyridyl)-1-butanone,

RAS: a proto-oncogene of the G-Protein type and its encoding gene, MYC: a regulatory gene and proto-oncogene family encoding transcription factors, RB: Retinoblastoma gene, FHIT: fragile histidine triad gene.

What cancers does smoking cause?

Smoking is the most important preventable cause of cancer worldwide. It is responsible for approximately ¼ of cancer-related deaths in Turkey and corresponds to almost one-fifth of all cancers. More than four out of five lung cancer cases are caused by smoking. Lung cancer has the lowest survival rate of all cancers. Smokers are 20 times more likely to develop lung cancer than non-smokers. It is the most common of cancer deaths in Turkey, and most of these deaths can be prevented by timely quiting smoking [33,34].

The link between smoking and cancer is very clear. It is known to cause at least 15 different types of cancer: mouth, pharynx (upper pharynx), nose and sinuses, larynx (larynx), esophagus (esophagus), liver, pancreas, stomach, kidney, intestine, ovary, bladder, cervix and some leads to other cancers such as leukemia types [35].

Activities carried out in the fight against tobacco in Turkey

- “Framework Convention on Tobacco Control (FCTC)”, the first international agreement in the fight against tobacco, was signed by our country on April 28, 2004 [33].
- The first “National Tobacco Control Programme”, prepared in cooperation with ministries, universities and non-governmental organizations, was published with the Prime Ministry Circular on 07 October 2006. “National Tobacco Control Program Action Plan 2008-2012”, “National Tobacco Control Program Action Plan 2015-2018”, “Youth Action Plan to Combat Tobacco”, “Provincial Tobacco Control Boards” were structured. In 2007, the Department of Combating Tobacco and Substance Addiction was established. ALO 171 Smoking Cessation Advice Line was put into service. In line with the Board Decision of the Tobacco and Alcohol Market Regulatory Authority (TAPDK), pictorial health warnings have been started to be used on cigarette packages [23].
- "International Protocol for the Prevention of Illegal Trade in Tobacco Products" was signed. In the 2013 and 2019 "Global Tobacco Epidemic Report", it was reported that Turkey is the country that fulfills all the M-POWER criteria [23].
- Established in 2018, the "High Council for Combating Addiction" has prepared a Tobacco Control Strategy Document and Action Plan. This plan is detailed in the titles of Reducing Demand for Tobacco Products, Reducing Availability of Tobacco Products and Coordination, Monitoring and Evaluation in Tobacco Control [23].

Environmental Risk Factors

With reference to health, the World Health Organization (WHO) defines the **environment** as all physical, chemical or biological factors outside the individual and all associated behaviors, but logically excludes unalterable natural environments from this definition [36]. As such, the definition is in principle restricted to those environmental components that can be changed (such as air pollution, electromagnetic fields, occupational risks, building/structural environment or agricultural methods) in order to actually reduce the environmental impacts on health. It excludes behaviors and lifestyles that are not related to the environment, such as the use of alcohol or tobacco, and similarly excludes parts of the social or cultural environment, genetic and unalterable natural environment. Therefore,

environmental interventions are key in reducing cancer incidence and mortality – including in the workplace – by preventing or reducing exposure to environmental carcinogens through individual prevention measures. Environmental factors at risk for cancer development typically affect the general population through exposures that cannot be directly controlled by the individual. These factors may be present in the environment physically (ionizing or non-ionizing radiation such as radon or exposure to ultraviolet radiation), chemical (asbestos, dioxins and other pollutants found in industrial emissions and passive smoking, pesticide residues in food and drinking water, arsenic or aflatoxin) such as pollutants or natural components) and biological carcinogens such as certain viruses. Carcinogenic effects in humans can occur through exposure to radiation, air pollution, components or pollutants in food or water, as well as with man-made consumer products (building paints, pesticides applied in gardens or playgrounds, chemicals used in cleaning homes and schools, toys, etc.).

Water: The most common carcinogens in water are heavy metals. Heavy metals are metals such as arsenic, lead, mercury, copper, zinc. Arsenic has extremely harmful effects on the body. In addition, there are heavy metals (selenium, copper, zinc) that must be found in trace amounts in the body. The deficiency as well as the excess of these heavy metals can cause harmful effects. Thanks to the development of environmental technologies, many pollutants can now be effectively removed from water, soil and air. Trihalomethanes (THM) chloroform, dichlorobromomethane (DCBM), chlorodibromomethane (CDBM) and bromoform (TBM) are natural organic-containing water chlorination by-products. Since chlorine is used as a disinfectant in the majority of drinking water treatment, THMs are formed in treated water. Apart from chloroform, THMs cause cancer in laboratory animals and also in humans [37,38].

Electromagnetic Field: According to the "Regulation on Control and Inspection on Determination of the Exposure Limit Values of the Intensity of Electromagnetic Fields Originating from Electronic Communication Devices According to International Standards", a security certificate is issued to the base stations if the places where people live and the pre-school and basic education institutions, including all buildings, gardens and outbuildings, can be found in a safe area, no establishment or living space is allowed within the safety distance [39].

Such exposures can occur in various ways and at various times throughout life, both at home and at school or workplaces. Children are generally more sensitive to environmental hazards than adults. In addition, occupational exposures of parents can increase the risk of developing cancer in their children (as studies of pesticides, benzene, asbestos and ionizing radiation have shown). Exposure may be widespread, such as in air pollution, or in a restricted area, such as near an industrial area. Although such exposures have been shown to be associated with a number of different neoplasms, they are known to be mainly associated with lung cancer, skin cancer or leukemia. Occupational health risks are also directly related to physical, chemical and biological factors in the environment and are often related to passive exposure and behaviors. Cancer types most frequently associated with occupational exposure and with strong evidence include lung, bladder, mesothelioma, larynx, leukemia, hepatic angiosarcoma, nasal and nasal cavity, and skin cancers [36].

The Monograph Program of the International Agency for Research on Cancer (IARC), an affiliate of the World Health Organization, identifies environmental factors with carcinogenic hazards to humans. The Monographs Programme evaluates different types of agents or substances, such as chemicals (e.g. formaldehyde), complex mixtures (e.g. air pollution), occupational exposures (e.g. working in coke production), physical agents (e.g. solar radiation), biological agents (e.g. hepatitis B virus) and personal habits (e.g. tobacco use) [40].

The International Agency for Research on Cancer (IARC) divides carcinogens into 4 groups according to the level of evidence (Table 4).

Table 4. Carcinogenicity Classification defined by International Agency for Research on Cancer

Group	**Definition**	**Level of evidence**
1	Carcinogenic to humans	There is enough evidence
2A	Likely carcinogenic to humans	Limited evidence for humans, sufficient evidence in animal experiments
2B	Suspected carcinogenic to humans	Limited evidence in humans and insufficient evidence in animal experiments, or insufficient or lack of evidence in humans and sufficient evidence in experimental animals
3	Not identifiable as a carcinogen to humans	Cannot be classified in any other group
4	Probably not carcinogenic to humans	No evidence of carcinogenicity in humans and experimental animals

To date, more than 900 possible agents have been studied, of which 120 were classified as Group1, 83 as Group 2A, 314 as Group 2B, and 500 as Group 3 [40].

The carcinogens most likely to affect human health in the US National Toxicology report are as follows:

- Aflatoxins
- Aristolochic Acids
- Arsenic
- Asbestos
- Benzene
- Benzidine

- Berilium
- 1,3 Butadian
- Cadmium
- Coal tar and coal tar pitch
- Coke oven emissions
- Silica crystal (respirable size)
- Erionite
- Ethylene oxide
- Formaldehyde
- Hexavalent chromium compounds
- Indoor emissions from domestic combustion of coal
- Mineral oils: Unprocessed or less processed
- Nickel compounds
- Secondhand tobacco smoke (environmental tobacco smoke)
- Fume
- Strong inorganic acid mists containing sulfuric acid
- Torium
- Trichloroethylene
- Vinyl chloride
- Sawdust

Air Pollution: Whether indoor or outdoor, **air pollution** is an important environmental health problem for developed countries as well as developing countries. Volatile organic compounds, nitrogen-containing and halogenated organic compounds, polycyclic aromatic hydrocarbons (PAH), toxic metals, and many by-products of incomplete combustion (eg dioxins) are all air-polluting carcinogens. IARC has classified outdoor air pollution as a human carcinogen (Group 1). The IARC assessment demonstrated an increased risk of lung cancer with increased exposure to particulate matter and air pollution. Studies reveal that exposure has increased in some parts of the world, especially in countries with high population density and rapidly industrializing, and according to the latest data, 223,000 lung cancer-related deaths have occurred worldwide due to air pollution [41].

Outdoor air pollution in urban settlements: Many of the air pollutants are released into the air from mining activities and other industrial plants, often after the use of coal or other fossil fuels for power generation, especially in developed countries, or from municipal landfills. Motor vehicles also contribute significantly to air pollution in urban settlements. Some substances in vehicle exhausts are considered carcinogenic to humans (Group 1) or possibly carcinogenic (Group 2A) by the IARC. Epidemiological studies have revealed that the risk of lung cancer is higher in individuals living in cities and those living close to industrial areas than those living in rural areas. Benzene found in gas stations and vehicles has been shown to cause Acute Myeloid Leukemia and is estimated to be associated with acute and chronic lymphoblastic leukemia, Hodgkin lymphoma, and Multiple Myeloma [36].

Indoor air pollution: The use of coal, wood, or other biomass for cooking or heating in many low- and middle-income countries is common practice, which not only increases indoor air pollution to high levels, but also contributes significantly to outdoor air pollution. Burning fossil fuels and wood in homes produces polycyclic aromatic hydrocarbon (PAH), increasing the risk of developing lung cancer and other types of cancer. Indoor emissions from domestic combustion of biomass (mainly wood) are classified as Group 2A by the IARC due to the presence of PAH and other carcinogenic compounds in wood smoke, as well as mechanistic evidence of wood smoke-induced mutagenicity and cytogenetic damage. There is epidemiological and experimental evidence that edible oil emissions during high-temperature frying pose a predisposing risk to cancer. There are also a number of studies showing the relationship between solid fuel use and larynx-pharynx-nasopharynx-nasal cavity and paranasal sinus cancers [36].

Passive smoking includes many of the components in cigarette smoke (arsenic, benzene, 1,3-butadiene, cadmium, PAH, etc.). 69 of these are carcinogenic and their usual association with lung cancer has been shown. There is also limited evidence of association with some other types of cancer (larynx, pharynx, nasal cavity, paranasal sinuses, cervix, breast, and gastrointestinal tract). Passive smoking contributes to both indoor and outdoor air pollution [36].

Asbestos: Asbestos is the general name for a group of naturally occurring inorganic fibrous silicates [42].

These fibers are found in soils and rocks in many parts of the world. They are mainly made of silicon and oxygen, but they also contain other elements. There are two main types of asbestos: **Chrysotile Asbestos** and **Amphibole Asbestos**. Both types of asbestos are linked to cancer.

Asbestos has been used as an insulating material since ancient times. Since the industrial revolution, asbestos has been used to insulate factories, schools, homes, and ships, and to make automobile brake and clutch parts, roof insulation, ceiling and floor tiles, cement, textiles, and hundreds of other products.

The use of asbestos has been banned in the European Union since 2005, but the ban does not cover the removal of existing asbestos and in some countries heavy use of asbestos continues.

All forms of asbestos are carcinogenic to humans, and stopping the use of all forms of asbestos is the most effective way to eradicate asbestos-related diseases [43,44].

Asbestos exposure, including chrysotile, causes lung, larynx, and ovarian cancer, as well as mesothelioma (cancer of the pleural and peritoneal layers). Currently, approximately 125 million people worldwide are exposed to asbestos in the workplace. It is estimated that about half of occupational cancer deaths are caused by asbestos [42,44,45].

There is also some evidence of a relationship between asbestos exposure and pharyngeal, stomach, and colorectal cancers [36].

Physical Exposures to Ionizing and Non-Ionizing Radiation: Radiation is ubiquitous in our environment and has natural or man-made sources. One of the most extensively studied carcinogens classified in Group 1 by the IARC, findings on ionizing radiation come from mining, military and industrial applications, or medical uses. Non-ionizing radiation includes electromagnetic fields, from static fields to radio waves, as well as microwaves, infrared, ultraviolet and visible radiation [36]. Ionizing radiation consists of electromagnetic waves (x-radiation and y-radiation) at the high-energy end of the electromagnetic spectrum and energetic subatomic particles (neutrons, β-particles, and alpha-particles) [46]. This type of radiation carries enough energy to liberate electrons from atoms and thus can break chemical bonds. The biological effects of ionizing radiation vary according to the amount of energy absorbed by the exposed organ or tissue.

Natural radiation exposure occurs through four main sources: cosmic radiation, terrestrial radiation, ingestion of soil and ground radionuclides, and inhalation of radon. Exposure to cosmic radiation is higher at higher altitudes. Exposure to natural radionuclides varies from region to region according to the geological area. Radon is a gas formed during the degradation of natural uranium in soil. Indoor radon exposure varies depending on the geological region, building construction, and household lifestyle. About half of natural radiation exposure worldwide is due to inhalation of radon.

Today, ionizing radiation covers a wide range of fields such as medicine, nuclear energy, research, manufacturing and construction, and this can result in environmental, occupational and medical exposures. Environmental exposures include nuclear waste from weapons tests, nuclear power plant accidents (such as Chernobyl and Fukushima), and routine releases from nuclear facilities. Medical radiation exposure occurs as a result of certain diagnostic procedures, such as radiography, nuclear medicine, and computed tomography, or as a result of treatment, often radiotherapy for the treatment of cancer. With the development of technology, the medical uses of radiation increased rapidly and spread widely.

The mechanisms by which radiation can cause carcinogenic changes include mutations, changes in gene structure or chromosomes, and differentiation in gene expression.

Evidence that ionizing radiation can cause cancer in humans comes from epidemiological studies, particularly studies of patients who received radiation for therapeutic reasons, and from studies of atomic bombing survivors. The time interval between exposure to ionizing radiation and the occurrence of an extreme increase in cancer risk ranges from a few years to several decades. In addition, the age of exposure, age and gender of the host influence the dose-risk relationship.

Radiofrequency Electromagnetic Fields: Radiofrequency electromagnetic fields (RF-EMF / Radiofrequency Electromagnetic Fields) are emitted from various sources. In terms of society, the most common sources in daily life are wireless communication devices and transmitters.

Cordless phones and other devices used in close proximity to the body produce exposure to an electromagnetic field close to 1, characterized by its specific absorption rate

(expressed in watts per kilogram of tissue weight). Like further transmitters in wireless local area networks, base stations of cordless and mobile phones, broadcast transmitters, and other people's mobile phones are far-field sources, and the most common exposure measurement is the accidental electric field (in volts per meter).

Mechanism of Causing Cancer: Since RF-EMF is located in the non-ionizing part of the electromagnetic spectrum, photon energy is too weak to ionize molecules. Thus, it does not cause direct DNA damage. It is known that RF-EMF absorption causes an increase in temperature in biological tissues. However, minimal temperature increases below regulatory limits are not expected to increase cancer risk. Despite numerous studies, a mechanism associated with carcinogenesis has not been consistently identified to date.

Given the research uncertainties, it would be appropriate to take precautionary measures. Keeping mobile phones away from the body during transmission is the most effective precaution that can be taken, as mobile phones are the most likely source of exposure and RF-EMF power decreases rapidly with distance from the source. This will result in a rapid reduction in exposure [46].

Solar rays and ultraviolet radiation: Solar radiation covers a wide wavelength range of photon energy in the electromagnetic spectrum. It includes ionizing radiation, ultraviolet (UV) radiation, visible light and infrared radiation [47].

UV radiation is classically divided into three types: UVA (315-400 nm wavelength range), UVB (280-315 nm wavelength range) and UVC (100-280 nm wavelength range).

Although solar UV radiation has beneficial biological effects such as enabling vitamin D synthesis, it also has undesirable effects such as sunburn, sunspot development, immunosuppression and inducing skin cancers.

Ultraviolet radiation causes DNA lesions in direct and indirect ways. This causes mutation, triggering inflammation and immunosuppression that mediate tumor growth.

Photocarcinogenesis is a complex, multistep process initiated by the formation of pyrimidine photoproducts, which itself leads to mutation formation (initial phase). These products activate the growth and progression of cancer cells by triggering the immunosuppression induced by ultraviolet. The incidence of skin cancers is increasing all over the world, especially in the elderly.

The main source of exposure to "ultraviolet radiation" for humans is solar radiation. In addition, many people use tanning devices (such as sun lamps and sun beds) that are artificial sources of UV radiation, in some occupational situations UV lamps are used for polymerization (typically in resin curing and coating) and germicidal UV lamps (for disinfection purposes). Special UV lamps are also used in the treatment of certain skin diseases such as vitiligo vulgaris, psoriasis and atopic dermatitis.

Welders should use personal protective equipment as there is ultraviolet radiation emission during the welding process.

The ozone layer in the stratosphere absorbs wavelengths of solar UV radiation shorter than 300 nm. Therefore, only UVA radiation and UVB with wavelengths longer than 300 nm reach the Earth's surface. Radiation reaching the Earth's surface consists largely of UVA (95%). The UVB component makes up only a small part (5%).

The IARC Monographs have classified UV-emitting tanning devices (sun lamps and sun beds) as carcinogenic to humans (Group 1). Although commercial tanning devices are banned in some states in America, all states and territories in Australia, and some other countries, many people continue to use them.

The most effective way to reduce the incidence of skin cancer is to avoid unnecessary sun exposure and to protect from sunlight by taking personal precautions such as wearing protective clothing, wearing a hat, applying sunscreen and staying in the shade. Limiting the time spent outside between 9:00 and 15:00, when sunlight intensity is at its maximum, will significantly reduce the risk of sun damage.

In summary, the most effective way to reduce the incidence of skin cancer is to avoid unnecessary sunlight exposure, to take protective measures when staying in the sun, and to stay away from tanning devices [47].

Radon: Radon formed as a result of the decay of natural radioactive uranium found in soil and rocks. It is a colorless, odorless, tasteless radioactive gas and can also be found in water [48,49].

Most of the radon source in buildings is the soil and rocks at the foundation of the building. Radon comes from all soils and rocks where radium is present and rises through the soil, being trapped under the building and creating pressure. With the pressure difference created, the radon gas under the building leaks into the buildings from the cracks in the concrete floor and walls, the gaps between the floor and the flooring, the pores of the brick walls, the installation pipe gaps. Radon gas can accumulate heavily, especially in basements and mines [49,50].

Since all waters, especially groundwater, contain certain amounts of uranium, there is radon gas in the waters. In addition, radon found in soils and rocks with which water is in contact can increase the radon content of the water as it seeps through pores and cracks and mixes with the water. In this sense, since groundwater is in contact with rock and soil for a longer time, its radon concentration is higher than in surface waters. This situation must be taken into consideration in areas where wells and spring water are used for drinking and cleaning purposes, and the radon content of the waters must be measured [51]. Epidemiological studies performed to date have not found an association between the consumption of drinking water containing radon and the risk of gastric cancer. Radon dissolved in drinking water can be released into indoor air. Simple and effective techniques are available to reduce the radon concentration in drinking water supplies using aeration or granular activated carbon filters [48]. Building materials are one of the factors that increase the radon level in closed areas. Studies show that with the mechanism called "external respiration", radon gas is constantly released from the building walls and building components to the indoor environment by diffusion and increases the amount of radon in the indoor environment. In addition, it has been revealed that in houses made of stone, brick or concrete, depending on the surface geology of the region, the external gamma rays are effectively absorbed by the walls and transferred into the house, thus increasing the indoor radon concentration [51].

Radon easily diffuses from the ground into the air, where it decays and produces more radioactive particles. When we breathe, particles build up on the cells lining the airways, where they can damage DNA and potentially cause lung cancer. Radon is the most important cause of lung cancer after smoking. It is estimated to cause 3–14% of all lung cancers in the country, depending on the average radon level and the prevalence of smoking in a country [48]. Based on ample evidence that it can cause lung cancer, the

IARC has classified radon as "carcinogenic to humans" (Group 1) [52].

Activities carried out in Turkey in the fight against environmental factors

- **Turkey Asbestos Control Strategic Plan was prepared.** The first studies to prevent asbestos exposure started in 2009. In this period, together with the Environmental Health teams of the Health Directorates, the villages were visited and the head people and citizens were interviewed, and the places where there could be contact with the soil were tried to be determined. In many of the places where asbestos was detected from the soil samples, studies were carried out by the Directorate, Governorship, Municipality, District Governorate and Provincial Directorates of the relevant Ministries to paint the houses, pave the roads, close the places where asbestos soil was brought, and prevent the people from using this soil. Especially many houses were painted, our citizens without financial situation painted their houses with the financial assistance of the District Governorships, many village roads were paved, the use of asbestos soil ("white soil") was prevented in many places, awareness and training activities were carried out.
- In 2012, with the participation of many academicians, **"Turkey Asbestos Control Strategic Plan"** studies were started and it was disseminated throughout the country. In the program, determination of the current situation throughout the country is named as Phase I, and carrying out the necessary improvement works is named as Phase II. Phase I studies carried out under the responsibility of our General Directorate have been completed and negotiations with the Ministry of Environment and Urbanization are continuing for Phase II studies.
- **Turkey Radon Mapping and National Radon Control Program** was developed. Measurements were made by the Turkish Atomic Energy Agency (TAEK) to determine the radon concentration in houses and building materials in Turkey. The main topic of discussion around the world is the Radon gas levels in the house rather than the building materials used. For this reason, countries should first identify the current situation, mapping across the country, and then initiate prevention programs in high-risk areas, as recommended by WHO. Measures such as adequate ventilation, fan facilities, awareness activities are measures that may be sufficient to keep indoor Radon at <300 Bq/m3. Within the scope of creating the **"Turkey Radon Map"** and then developing the **"National Radon Control Program",**

improvement studies will be started with the relevant parties in places with radon measurements above the standard values determined by WHO, and awareness, education, etc. activities will be carried out.

- **Monitoring and Evaluation of the Health Effects of Electromagnetic Fields:** As one of the 24 active members of IARC, Turkey closely follows the scientific developments on the subject and shares them with the public. Depending on the advancement of technology, it is predicted that while the field strengths required for communication of the devices will decrease, on the other hand, communication tools with different frequencies and intensities will be brought to the agenda with the new systems. Due to the increase in the field intensity of these devices and health problems such as possible cancer, studies in the scientific world and the studies of WHO, ICNIRP, IARC and BTK are closely followed.
- **Health Cost of Air Quality Program**
- **Use of Electronic Nose Tests in Lung Cancer Screening:**
    - Lung cancer is the leading cause of cancer death in both women and men worldwide.
    - Lung cancer is a type of cancer that results in death within 5 years in 86% of patients, even with the most advanced treatment methods. While the 5-year survival is 70% in those diagnosed in Stage 1 with early diagnosis, this value drops to 20% in those diagnosed in Stage 3. For this reason, screening test studies for early diagnosis in lung cancer have been the subject of many studies, and some tests such as PCR-based sputum analysis, Tomography, Fluorescent Bronchoscopy and Electronic Nose have been included in studies in this field.
    - Although studies on the use of sputum cytology and lung radiography as a screening test have shown that the survival time is prolonged with the use of these methods in screening, it has not been concluded that a decrease in mortality due to lung cancer has been achieved with both methods. Therefore, the use of these methods in lung cancer screening is not considered appropriate. Apart from these, the effectiveness of low-dose lung tomography, some blood markers, and bronchoscopic examinations in lung cancer screening have been the subject of various studies. Among these methods, it was concluded that bronchoscopy has high sensitivity and

specificity in lung cancer screening, but it is not suitable for screening because it is an invasive method.

- Some of the advantages suggested in the use of Electronic Nose analysis in lung cancer screening can be summarized as follows:
  - It is a non-invasive method.
  - It can be easily applied to everyone, including patients in advanced stages.
  - It has the feature of being repeated in short intervals.
- In addition to the advantages of analyzing the exhaled air with the Electronic Nose method, it also has a disadvantage because it contains many compounds that need to be analyzed and is a very complex process.
- 1003 TÜBİTAK Project "Electronic Nose in Early Diagnosis of Lung Cancer", created in cooperation with Hacettepe University, METU, TÜBİTAK MAM, General Directorate of Public Health Cancer Department and Kütahya Dumlupınar University, on lung cancer screening with Electronic Nose tests has been accepted and the studies are continuing.

RESOURCES

1. 2013-2018 National Cancer Control Plan. T.R. Ministry of Health. Türkiye Halk Sağlığı Kurumu.http://www.iccpportal.org/sites/default/files/plans/ulusal_Kanser_Kontrol_Plani_2013_2018.pdf 8.3.2016. 2. Globocan 2.
2. Cappellani A, Di Vita M, Zanghi A, Cavallaro A, Piccolo G, Veroux M, Berretta M, Malaguarnera M, Canzonieri V, Lo Menzo E. Diet, obesity and breast cancer: an update. Front Biosci (Schol Ed). 2012; 4:90-108.
3. Food Security and Nutrition Status in the World 2017 Report
4. https://www.turkiyeklinikleri.com/article/tr-beslenme-ve-kanser-86295.html.
5. Özcan Y., Demir G. Sağlıkta ve Hastalıkta Beslenme Sempozyum Dizisi, No:42, 2004; (2):45-57
6. Gaddy JA, Radin JN, Loh JT, Zhang F, Washington MK, Peek RM Jr, Algood HM, Cover TL. High dietary salt intake exacerbates Helicobacter pylori-induced gastric carcinogenesis. Infect Immun. 2013;81(6):2258-67.
7. Prof. Dr. Hakan Akbulut/Ankara Üniversitesi Tıp Fakültesi Tıbbi Onkoloji Bilim Dalı, Tüba-Gıda, Beslenme ve Kanserin Önlenmesi Sempozyumu Raporu, 2015.

8. Diet, nutrition and the prevention of cancer, Timothy J Key at all, Public Health Nutrition: 7(1A), 187–200.
9. Noelle K. LoConte et. al Alcohol and Cancer: A Statement of the American Society of Clinical Oncology.
10. Praud D, Rota M, Rehm J, et al: Cancer incidence and mortality attributable to alcohol consumption. Int J Cancer 138:1380-1387, 2016.
11. Nelson D.E., Jarman DW, Rehm J, et al: Alcohol-attributable cancer deaths and years of potential life lost in the United States. Am J Public Health 103:641-648, 2013.
12. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/490584/COC_2015_S2 Alcohol_and_Cancer_statement_Final_version.pdf
13. Van't Veer P, Kampman E: Food, Nutrition, Physical Activity, and the Prevention of Cancer: A Global Perspective. Washington, DC, World Cancer Research Fund/American Institute for Cancer Research, 2007.
14. World Cancer Research Fund: Continuous update project report: Diet, nutrition, physical activity and liver cancer. wcrf.org/liver-cancer-2015.
15. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans: Personal habits and indoor combustions, in A Review of Human Carcinogens. Lyon, France, 2009).
16. https://www.cancer.net/navigating-cancer-care/prevention-and-healthy-living/alcohol.
17. https://www.who.int/ncds/surveillance/steps/WHO_Turkey_Risk_Factors_A4_TR_19.06.2018.pdf
18. https://www.resmigazete.gov.tr/eskiler/2013/06/20130611-1.htm
19. https://www.mevzuat.gov.tr/Metin.Aspx?MevzuatKod=9.5.18711&MevzuatIliski=0&sourceXmlSearch=
20. https://www.gib.gov.tr/fileadmin/haberler/BANDROL_TEBLIG_TAS.htm)
21. https://www.cdc.gov/cancer/tobacco/index.htm.
22. .https://tobaccoatlas.org/
23. https://hsgm.saglik.gov.tr/depo/birimler/tutun-mucadele-bagimlilik-db/tutun/Tutun_Faaliyet_Raporu_2018_20.08.2019.pdf.
24. Doll R. Uncovering the effects of smoking: historical perspective. Stat Methods Med Res 1998; 7:87–117. Tobacco and Cancer: Recent Epidemiological Evidence.
25. P. Vineis, et al Journal of the National Cancer Institute, Vol. 96, No. 2, January 21, 2004.
26. https://apps.who.int/iris/bitstream/handle/10665/161991/9789241508469_eng.pdf.
27. U.S. Department of Health and Human Services. The Health Consequences of Involuntary Exposure to Tobacco Smoke: A Report of the Surgeon General. Atlanta, GA: US Dept of Health and Human Services, Centers for Disease Control and Prevention, National Center

for Chronic Disease Prevention and Health Promotion, Coordinating Center for Health Promotion, Office on Smoking and Health; 2006.

28. 28].Parkin DM, Pisani P, Lopez AD, Masuyer E. At least one in seven cases of cancer is caused by smoking. Global estimates for 1985. Int J Cancer 1994; 59: 494–504.
29. Molarius A, Parsons RW, Dobson AJ et al. Trends in cigarette smoking in 36 populations from the early 1980s to the mid- 1990s: findings from the WHO MONICA Project. Am J Public Health 2001; 91: 206–12.
30. Peto R, Darby S, Deo H, Silcocks P, Whitley E, Doll R. Smoking, smoking cessation, and lung cancer in the UK since 1950: combination of national statistics with two case–control studies. BMJ 2000; 321: 323–9.
31. https://www.ncbi.nlm.nih.gov/books/NBK53010/.
32. Hecht SS. Tobacco smoke carcinogens and lung cancer. J Natl Cancer Inst 1999; 91: 1194–210.
33. http://www.kanservakfi.com/sigara-ve-kanser-132.html
34. https://www.fda.gov/tobacco-products/health-information/tobacco-use-and-mens-health.
35. https://www.cancerresearchuk.org/about-cancer/causes-of-cancer/smoking-and-cancer/how-does-smoking-cause-cancer.
36. An Overview of the Evidence on Environmental and Occupational Determinants of Cancer. International Conference on Environmental and Occupational Determinants of Cancer: Interventions for Primary Prevention, Asturias, Spain, 17-18 March 2011, WHO. https://www.who.int/phe/news/events/international_conference/Background_science.pdf Date of Access: 13.02.2020).
37. https://www.uplifers.com/suda-bulunan agir-metaller-ve-etkileri-ictiginiz-su-ne-kadar-saglikli/Oya Milli SÜLÜN.
38. https://www.turkiyeklinikleri.com/article/en-agir-metaller-ve-kanser-riski-77344.html
39. Regulation on Determination of Exposure Limit Values of Electromagnetic Field Intensity Originating from Electronic Communication Devices According to International Standards, Control and Supervision. Official Gazette Date: 21.04.2011, Official Gazette Number: 2791/2
40. Agents Classified by the IARC Monographs, Volumes 1–125. International Agency of Cancer Research. https://monographs.iarc.fr/agents-classified-by-the-iarc/ DOA: 13.02.2020]
41. IARC: Outdoor air pollution a leading environmental cause of cancer deaths. International Agency for Research on Cancer. https://www.iarc.fr/wp-content/uploads/2018/07/pr221_E.pdf Erişim Tarihi: 14.02.2020.

42. Asbestosis and Cancer Risk.American Cancer Society. https://www.cancer.org/cancer/cancer-causes/asbestos.html DOA: 15.02.2020.
43. Arsenic, Metals, Fibres, and Dusts. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans Volume 100C. https://publications.iarc.fr/Book-And-Report-Series/Iarc-Monographs-On-The-Identification-Of-Carcinogenic-Hazards-To-Humans/Arsenic-Metals-Fibres-And-Dusts-2012 Erişim tarihi: 16.02.2020.
44. Asbestos: elimination of asbestos-related diseases. WHO. https://www.who.int/news-room/fact-sheets/detail/asbestos-elimination-of-asbestos-related-diseases Erişim Tarihi: 16.02.2020
45. Occupation The need for continuing vigilance. World Cancer Report, Cancer research for cancer prevention.World Cancer Report 2020 pdf. http://publications.iarc.fr/Non-Series-Publications/World-Cancer-Reports/World-Cancer-Report-Cancer-Research-For-Cancer-Prevention-2020 doa: 16.02.2020).
46. Ionizing radiation and radiofrequency electromagnetic fields. Further clarification of particular risks. Section 2, Chapter 2.5.World Cancer Report 2020 pdf. Cancer research for cancer prevention. Edited by Wild CP, Weiderpass E, Stewart BW. IARC Publications, Lyon, France. http://publications.iarc.fr/Non-Series-Publications/World-Cancer-Reports/World-Cancer-Report-Cancer-Research-For-Cancer-Prevention-2020 DOA: 16.02.2020].
47. Sunlight and ultraviolet radiation. Affecting skin cancer incidence in many countries. Section 2, Chapter 2.4. World Cancer Report 2020 pdf. Cancer research for cancer prevention. Edited by Wild CP, Weiderpass E, Stewart BW. IARC Publications, Lyon, France. http://publications.iarc.fr/Non-Series-Publications/World-Cancer-Reports/World-Cancer- Report-Cancer-Research-For-Cancer-Prevention-2020 Erişim Tarihi: 18.02.2020
48. Radon and Health.WHO. https://www.who.int/news-room/fact-sheets/detail/radon-and-health Erişim Tarihi: 19.02.2020
49. Radon Outreach Kit. National Radon Program. http://www.epapsa.com/images/radon_outreach_kit.pdf doa: 19.02.2020.
50. Radon And Health. WHO. https://www.who.int/ionizing_radiation/env/Radon_Info_sheet.pdfdoa: [19.02.2020].
51. Radiation, radon (rn) and public health. Yüksel ÖRGÜN İTÜ Maden Fakültesi Jeoloji mühendisliği Bölümü Nilgün ÇELEBİ Çekmece Nükleer Araştırma ve Eğitim Merkezi. Haber bülteni TMMOB Jeoloji Mühendisleri Odası.

https://www.jmo.org.tr/resimler/ekler/03f20a42de5f061_ek.pdf?dergi=HABER%20B%DCLTEN%DD doa: 19.02.2020

52. Radon and Cancer. American Cancer Society. https://www.cancer.org/cancer/cancer-causes/radiation-exposure/radon.html doa: 19.02.2020.

3.5. AWARENESS RAISING ACTIVITIES IN THE WORLD AND IN TURKEY

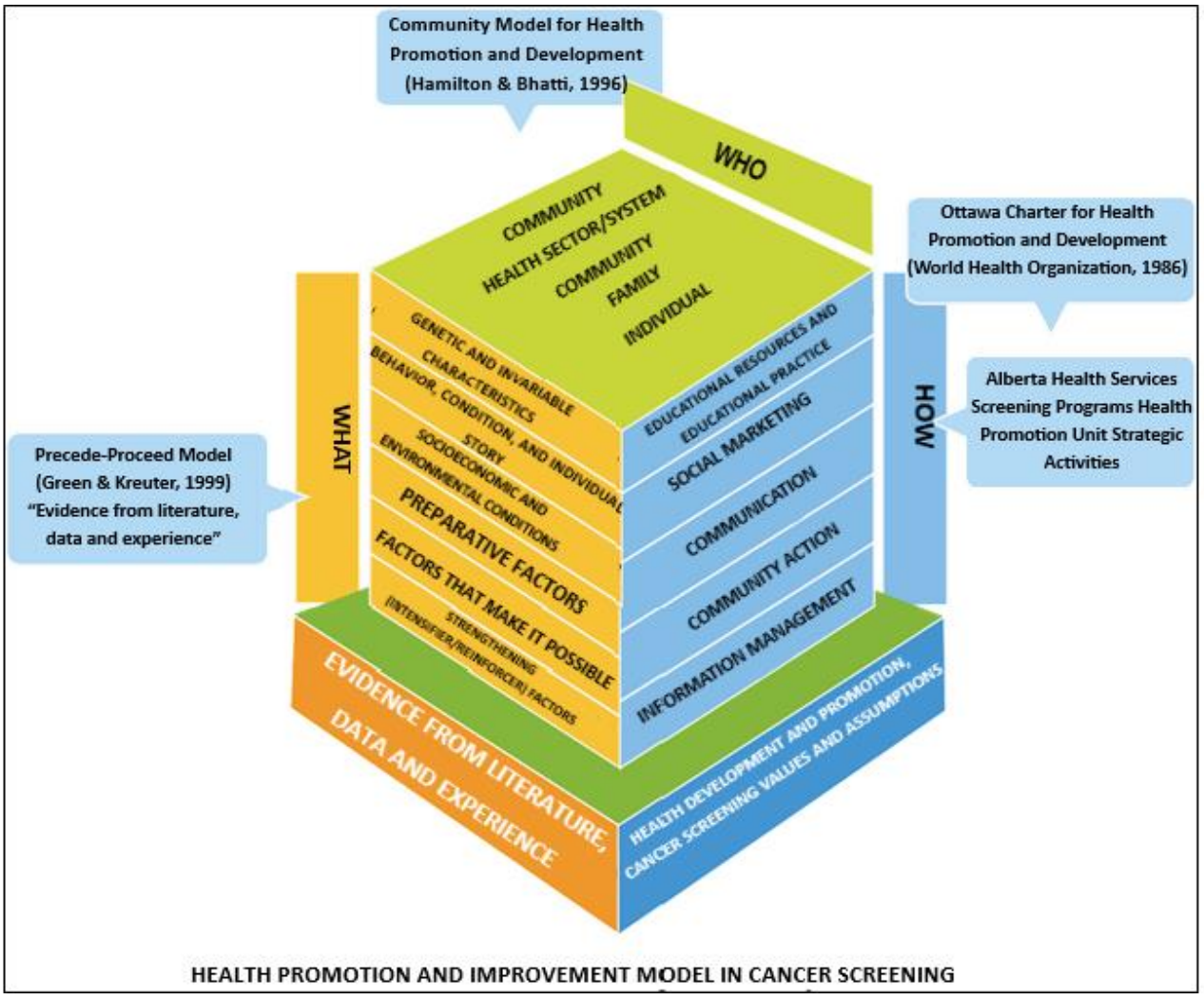
Cancer prevention strategies include reducing or eliminating exposure to risk factors, and conducting screening studies for early diagnosis in secondary prevention. In this context, in addition to reducing the impact of risk factors on human health and early diagnosis and treatment, it is very important to increase the awareness of the society, to use these services and to implement prevention strategies. Low health literacy of the population and therefore low cancer awareness (knowledge or belief about cancer symptoms, risk of developing cancer, risk factors, effectiveness of treatment or effectiveness of early detection strategies) is a risk factor for late diagnosis [1]. Tertiary prevention focuses on the treatment and physical, mental and social rehabilitation processes of individuals. It has been observed that awareness-based intervention programs in this period produced effective and positive results in reducing the symptoms experienced by different cancer patients during/after treatment [2,3,4].

Primary prevention studies aimed at reducing risk factors in cancer give their results late. This is because cancer is a multifactorial disease and it is difficult for individuals to acquire healthy lifestyle behaviors to reduce risk factors. For this reason, screening programs for early diagnosis are implemented in many countries apart from these studies. It is necessary to evaluate whether early diagnosis programs are accepted and used by the society and whether service delivery quality measures are established or followed [5]. In examining the quality, inputs, processes, outputs and outputs (short, medium and long term) with a system model, the following should be considered: *The target population's accessibility (inclusion and timing) to all services of the early detection program, the acceptability of the services and the availability of appropriate standards, the service providers' competencies (knowledge and skills), continuity of activities (ease of integration, coordination and progression), effectiveness of programs (improving health status and producing the best results at the lowest cost), etc.*

The whole process and practices of individuals to increase their control over their own health and to improve their health is called *health promotion* [6]. It is necessary to address five main strategies in health promotion: creating healthy public policies, creating health-supporting environments, strengthening community participation, improving the personal skills of the community, and reorganizing health services in line with needs. One of the important tools of health promotion is health education. With health education, it is tried to ensure that individuals develop knowledge, attitude and behavior changes in the desired direction about health. Perception of risk for their own health is effective in creating health behavior in the desired direction in individuals. The term risk perception is defined as the perceived susceptibility to a health threat. When we look at cancer awareness, it covers the dimensions of risk perception, perceived probability of cancer, vulnerability, and health severity of cancer cases. According to the perceived risk dimension, which protective behavior they should do (for example, healthy eating, physical activity, getting scans, etc.) and their self-efficacy to be able to do these behaviors, what kind of deficiencies/difficulties they will cause in their life, affect the behavior and the continuity of the behavior. Individuals' perceptions of cancer are that if the risk is low, they do not intend to do the recommended behavior and not do it. Individuals tend to give maladaptive responses (for example, denial) if the perceived risk is high, but they do not have the self-efficacy and opportunity to do what they need to do for various reasons. If an individual's health literacy is low, their perceived risk and behavioral self-efficacy are also low [7,8]. Increasing the level of health literacy through health education and appropriate health communication strategies to be given to the society positively affects awareness in protecting and improving health. *Health literacy* is defined as the cognitive and social skill capacity required for individuals to access, understand and use health-related information in order to maintain and develop good health. The health literacy level of the society affects its ability to implement the right health behaviors. The level of health literacy varies according to socio-demographic characteristics. While the level of health literacy is limited/insufficient at the rate of 48% in Europe, it is limited/insufficient at 68.9% in Turkey [9,10]. For this reason, it is very valuable to plan cancer awareness studies according to the characteristics of the society.

The health promotion model in cancer screening defines who does what and how (Figure 3).

Figure 3. Health Improvement Model in Cancer Screening: What, Who, How



1. The **"what"** component of the health promotion model in cancer screening: This component includes the determinants of general health. These determinants, especially the social determinants of health, are called "factors associated with cancer screening". There are six groups of these factors associated with cancer screening.
    a. The first three groups; "genetic and unalterable traits", "behaviour, situation and personal characteristics" and "socioeconomic and environmental conditions" indicate who should receive cancer screening awareness interventions.

It tries to explain why individuals do not use screening programs or what needs to happen for individuals to be screened.

b. The last three groups are predisposing, activating and reinforcing factors. It is specific to the awareness and practices of cancer screening programs. These are the factors that cancer screening awareness interventions aim to change.

2. The **"how"** component of the health promotion model in cancer screening: Includes categories of strategic activities used to promote cancer screening. It aims to increase cancer screening at the population level by improving knowledge, influencing positive attitudes, and increasing awareness and use behavior in cancer screening. Includes educational resources and strategic activities in education, social marketing, communications, community action and knowledge management.
    a. Educational resources and training involve two types of activities.
        i. The first type of activity is the development and dissemination of information resources on cancer screening. These resources include brochures, fact sheets, posters, presentations, and informational materials about breast, cervical and colorectal cancer screening.
        ii. The second type of activity is education. The training includes sessions and workshops that provide information about cancer screening to healthcare professionals and the community (eg nurses, health promoters and educators, physician, etc.).
    b. Social marketing activities aim to create an environment that promotes cancer screening by improving cancer screening knowledge, attitudes, values and behaviors.
    c. Examples of communication activities are health information hotlines, correspondence (letters, articles and advertisements), print communication, websites, e-mails, online communication and telephone communication.
    d. Community activities provide support to community groups interested in promoting cancer screening to health departments.

The first step is to assist organizations interested in cancer screening with resources and expertise to meet their needs and goals. Such assistance is usually carried out on a short-term basis and in the form of consultations. The second phase is to communicate with community-based organizations through consultations to assist these groups with planning.

The third phase is to collaborate with community-based organizations to implement ongoing and sustainable cancer screening awareness activities in their communities. Knowledge management is "a set of tools and practices that enable people to create knowledge and share and apply what they know to increase effectiveness.

3. The "**who**" component of the health promotion model in cancer screening: Defines who should be reached through cancer screening awareness activities and who should be involved in carrying out these activities. These are evaluated in terms of society, health sector/system, society, family and individual.

Cancer awareness studies are carried out in many countries around the world. These studies cover activities at the individual and societal level. Evaluating 2557 articles, 35 studies at the individual level and 10 studies at the societal level to evaluate the effectiveness of intervention programs to increase cancer awareness, J Austoker et al. found that specific information was more effective than general information in individual activities [11]. There are many differences between societies living in Western and Asian countries in terms of culture, community identity, community participation and belonging. In a study involving a multicenter, multi-component community intervention to promote breast cancer screening mammography for women living in an urban community in Korea, awareness studies were shown to be effective in reducing misconceptions about breast cancer [12]. A systematic review of eight hundred and sixty-seven (867) articles found that breast cancer awareness initiatives increased breast self-examination behaviors and the likelihood of participation in breast cancer screening [13]. In a systematic review of 22 studies examining the impact of media interventions on knowledge and attitudes about cancer screening and early detection of cancer in Asian countries, positive results were found especially for cervical cancer, and media campaigns were shown to be effective [14]. In a review evaluating interventions applied to increase participation in cancer screening services, 71 intervention studies were examined and it was seen that 58 of them had positive effects on increasing participation in cancer screening services, providing an absolute increase of 2-20% [15]. In a study that aimed to determine the impact of health education on cervical cancer and screening awareness, knowledge

and perception among women in rural Nigerian communities, interventions were shown to raise awareness of cervical cancer and screening to 100%. It has been shown
to increase the rate of women with very good knowledge on this subject from 2% to 70.5%, and the rate of women with good perception from 5% to 95.1% [16]. A large-scale study conducted to promote the early diagnosis of breast, bowel and lung cancers aimed to raise public awareness of cancer. In addition, activities such as billboards, posters and brochures, creating exhibition areas in public spaces, creating theater, musical or comedy productions were organized and the participation of 436,000 people was ensured. As a result, according to cancer types
A significant increase of 8-12% has been shown [17]. In the Center for Disease Control and Prevention's (CDC) community guide on cancer screening, it is recommended to increase reminder messages, printed materials and videos, one-on-one training, screening services and practitioners for breast, cervical and colorectal cancers; group training, reducing barriers and out-of-pocket expenditures are recommended as breast cancer intervention strategies (Figure 4) [18]

Figure 4. The Effectiveness of Intervention Strategies in Cancer Screening

INTERVENTION STRATEGIES	RESULTS		
BREAST, CERVIX, COLORECTAL CANCER SCREENING INCREASED			
PATIENT-CENTERED SCREENING INTERVENTION STRATEGIES			
INTERVENTION	**BREAST CANCER**	**CERVICAL CANCER**	**COLORECTAL CANCER**
Reminder messages (phone message, postcard, e-mail)	o	o	o
Incentive	◊	◊	◊
Printed materials such as letters, brochures and newsletters	o	o	o
Mass media	◊	◊	◊
Group training	o	◊	◊
One-to-one training	o	o	o
Reducing structural barriers	o	◊	o
Reducing individual's out-of-pocket expenses	o	◊	◊
MULTI-COMPONENT INTERVENTION STRATEGIES			
	o	o	o
SERVICE PROVIDER-FOCUSED SCREENING INTERVENTION STRATEGIES			
Evaluation and feedback of service providers	o		
Motivation of service providers	◊		
Reminder and recall systems of service providers	o		

O SUGGESTED ◊ INSUFFICIENT

In Turkey, awareness activities are held in order to increase the knowledge and awareness level of the society about cancer and to create behavior change. These activities

are carried out intensively on predetermined special days, weeks or months. January is Cervical Cancer Awareness Month, February 4 is World Cancer Day, March is Colon Cancer Awareness Month, April 1-7 is National Cancer Week, September 15 is World Prostate Cancer Day, October is Breast Cancer Awareness Month, and November is Lung Cancer Awareness Month. In these activities, activities that will attract the attention of the society, which include information and messages, are held (walking, raffle, dance, concert, etc.).

Conclusion

Community awareness activities, which aim to prevent cancer, participating in screening programs, and being conscious in treatment processes, should be organized by recognizing the cultural/social and economic factors of the society. Since individuals' high general health literacy will increase the effectiveness of these studies, they should be carried out together with health literacy goals. Developing intervention programs by defining what, how and by whom to change behavior in the society and improve health will increase positive outcomes. Evaluation of the short, medium and long term effects of the developed intervention programs and awareness studies will contribute to new regulations and new programs.

In addition to the integrated and coordinated work of all health services in intervention studies aimed at raising the public's awareness of cancer, the approach and cooperation of other stakeholders to increase community participation under the leadership of health services will increase the effectiveness and efficiency of these studies.

RESOURCES

1. Ramirez et al., 1999; MacDonald et al., 2004.
2. Cennet Yastıbaş, Gülay Dirik, Kanser ve Farkındalık Temelli Müdahale Programları: Sistematik Derleme, Psikiyatride Güncel Yaklaşımlar-Current Approaches in Psychiatry 2018; 10(3):385-403 doi: 10.18863/pgy.357261.
3. World Health Organization. (2006). Cancer control: knowledge into action: WHO guide for effective programmes (Vol. 2).
4. World Health Organization. World Health Organization. (2002). National cancer control programmes: policies and managerial guidelines. World Health Organization.
5. World Health Organization. (2017). Guide to cancer early diagnosis.

6. WHO, 1986, Ottowa Charter.
7. De Hoog N, Stroebe W, de Wit JBF: e impact of vulnerability to and severity of a health risk on processing and acceptance of fear-arousing communications:Ameta-analysis. ReviewofGeneralPsychology 2007, 11:258-285.
8. Ruiter RAC, Abraham C, Kok G: Scary warnings and rational precautions: A review of the psychology of fear appeals. Psychology & Health 2001, 16:613-630.
9. TC Sağlık Bakanlığı Sağlığın Geliştirilmesi Genel Müdürlüğü Türkiye Sağlık Okuryazarlığı Düzeyi ve İlişkili Faktörleri Araştırması Yayın No 1103 Ankara 2018.
10. Sørensen K, Pelikan JM, Röthlin F et al. Health literacy in Europe: comparative results of the European health literacy survey (HLS-EU) European Journal of Public Health, Volume 25, Issue 6, December 2015, Pages 1053–1058.
11. J., Austoker, C.Bankhead, and A J Ramirez.,Intervention to prmote cancer awareness and early presentation:systematic review.Biritish Journal of Cancer.
12. Park K., Hong W.H., Kye S.Y…et all, Community-based intervention to promote breast cancer awareness ans screening: The Korean experience.,BMC Public Health 2011, 11;468.
13. Anastasi N. and Lusher J. The impact of breast cancer awareness interventions on breast screening uptake among women in the United Kingdom: A systematic review. Journal of health psychology 2019, 24(1), 113-124.
14. Schliemann D., Su T.T., Paramasivam D and Donnelly M., Effectiveness of Mass and Small Media Campaigns to Improve Cancer Awareness and Screening Rates in Asia: A systematic review. Journal of Global Oncology 2018, 4(2):57.
15. Duffy S.W., Myles, J. P., Maroni, R and Mohammad, A. Rapid review of evaluation of interventions to improve participation in cancer screening services. Journal of Medical Screening, 2017. 24(3), 127-145.
16. Abiodun O.A., Olu-Abiodun O.O., Sotunsa J.O and Oluwole F.A., Impact of health education intervention on knowledge and perception of cervical cancer and cervical screening uptake among adult women in rural communities in Nigeria,2014. BMC public health, 14(1), 814.
17. Promoting early diagnosis of breast, bowel and lung cancers, First report, 2010/11 local projects, https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/212788/2900105_Cancer_BreastBowelLung_acc2.pdf Erişim Tarihi: 03.06.2020.
18. https://www.thecommunityguide.org/sites/default/files/assets/What-Works-Factsheet-CancerScreening.pdf)

SECTION 4

SECONDARY PROTECTION

4.1. Cancer Screenings

4.1.1. What is Screening? Why is Cancer Screening Done?

Examination of asymptomatic people for the control of diseases is called "screening". Health screenings are programs that are applied to healthy people at regular intervals in order to detect diseases early and reduce morbidity and mortality [1].

In public health practices, it is a common practice to examine and examine groups that do not have symptoms but are at risk for disease or diseases for the purpose of early diagnosis and treatment of the disease. The purpose of screening tests is not to diagnose, but to reveal a positive finding, if any, in the early period to confirm the diagnosis with more advanced methods [1]. Screening tests are applied to people who have no complaints but are at risk. Unlike the clinical diagnosis, the suspects are separated in the scans and then the full diagnosis is made with further examinations. The treatment of people with the disease caught by screening programs is both easier and more cost effective [2].

The aim of screening is to identify those with suspected disease as accurately as possible and to make an early diagnosis before symptoms develop. Identification of disease indicators at an early stage can lead to the development of treatment that will benefit society in a short time [2]. It was first brought to the agenda by Wilson and Jungner in 1968 in which situations screening would be appropriate in societies [1]. According to the Wilson-Jungner criteria of the World Health Organization, diseases to be included in national screening programs should have the following characteristics.

1. It should be an important health problem with a high frequency of disease in the community,

2.There should be sufficient information about the natural course of the disease to be screened. It should be screenable in the early stages and have a latent or early symptomatic period.

3. Scanning should be a continuous process and an appropriate test procedure should be followed,

4. For the disease to be screened, there should be ethical, safe, appropriate and practical test and examination methods and these should be accepted by the society.

5. The intervals at which the test will be repeated should be clearly determined,

6. There should be an appropriate treatment method for the improvement of the patients found as a result of the screening,

7. The selectivity and sensitivity of the tests should be as high as possible,

8. There must be an agreed method for which patients should be treated,

9. The test cost-benefit ratio should be economically balanced.

The situation that adds value to screening programs depends on the existence of the investigated factor and the existence of acceptable and effective measures to combat the problems it causes. If the correction of any pathology or the damage cannot be prevented or reduced, screening the society for such a condition will not be beneficial. In order for screening programs to be useful, they must be accepted by the society and must have high community participation [2]. For this reason, it is important for community participation that people know the harm of the disease to health and that each person accepts the possibility of getting this disease. If a disease is detected in the person, it is necessary to have the belief that the measures to be taken will positively affect the disease process. On the other hand, it is important for the success of the screening program that the screening program is suitable for the determined target group, supported by health professionals and is cost effective. Participation of more than 70% of the target population to be screened is essential [3]. The cost of a screening program has to be balanced against the number of cases detected and the consequences of not screening.

Many factors affect the finding of previously undiagnosed and unknown cases as a result of screening in a society and the benefit of screening them. The test should be able to reveal the real patients in the screened population, and the method should be able to accurately determine how many of the healthy ones, as well as the disease should have a feature that is common, causing death or crippling. Inexpensive, easy, fast, effective and reproducible, if possible, a previous search should be done on this subject [4]. Screening programs are an important component of preventive health practices that can reduce mortality.

Screening should not be viewed as a process that performs a specific test, examination or procedure. The screening process includes a system to inform and invite the target population, the implementation of screening tests, referral for further testing among those with test results and abnormal test results, and ensuring access to

effective treatment for timely pathological diagnosis, staging and routine evaluation, and improvement of the process. 4].

Cancer is a proliferative and invasive disease of hundreds of different tissues that has emerged with molecular mechanisms. Cancer is a general name and consists of hundreds of diseases with different clinical courses and different treatment responses. The cancer burden continues to grow globally, placing enormous physical, emotional and financial strain on individuals, families, communities and health systems [5]. Many health systems in low- and middle-income countries are not prepared to manage this burden, and many cancer patients globally do not have access to timely, quality diagnosis or treatment.

Each type of cancer has its own etiology, risk factors, diagnosis and treatment methods. Therefore, early diagnosis and screening strategies also vary according to cancer types. While early diagnosis and screening is recommended for some cancer types (eg breast, large intestine, cervix, prostate) it is not recommended for some cancer types (eg pancreas, thyroid, bladder) [5]. The issue of which cancer screening program will be applied, especially the World Health Organization (WHO) criteria determined for screening programs,

- It should also be shown that the screening method to be applied will reduce the cancer burden in the country,
- The screening program to be implemented should be a part of a holistic cancer control program [7].

Cancer screening is a complex public health strategy that requires additional resources, infrastructure and coordination. Screening programs should only be undertaken when their effectiveness has been proven, resources are sufficient to cover nearly the entire target group, health facilities are available to follow up on those with abnormal results to confirm diagnoses and provide treatment, and the prevalence of the disease is high enough to justify screening efforts and costs [5]. When planned, appropriately funded, and implemented effectively, screening can reduce deaths from cancer and, for some types of cancer, also reduce the risk of developing cancer [5]. The World Health Organization recommends population-based screening programs for catching cancer cases at early stages

in breast, cervical and colorectal cancers. However, states that studies should be part of a holistic cancer control program [5].

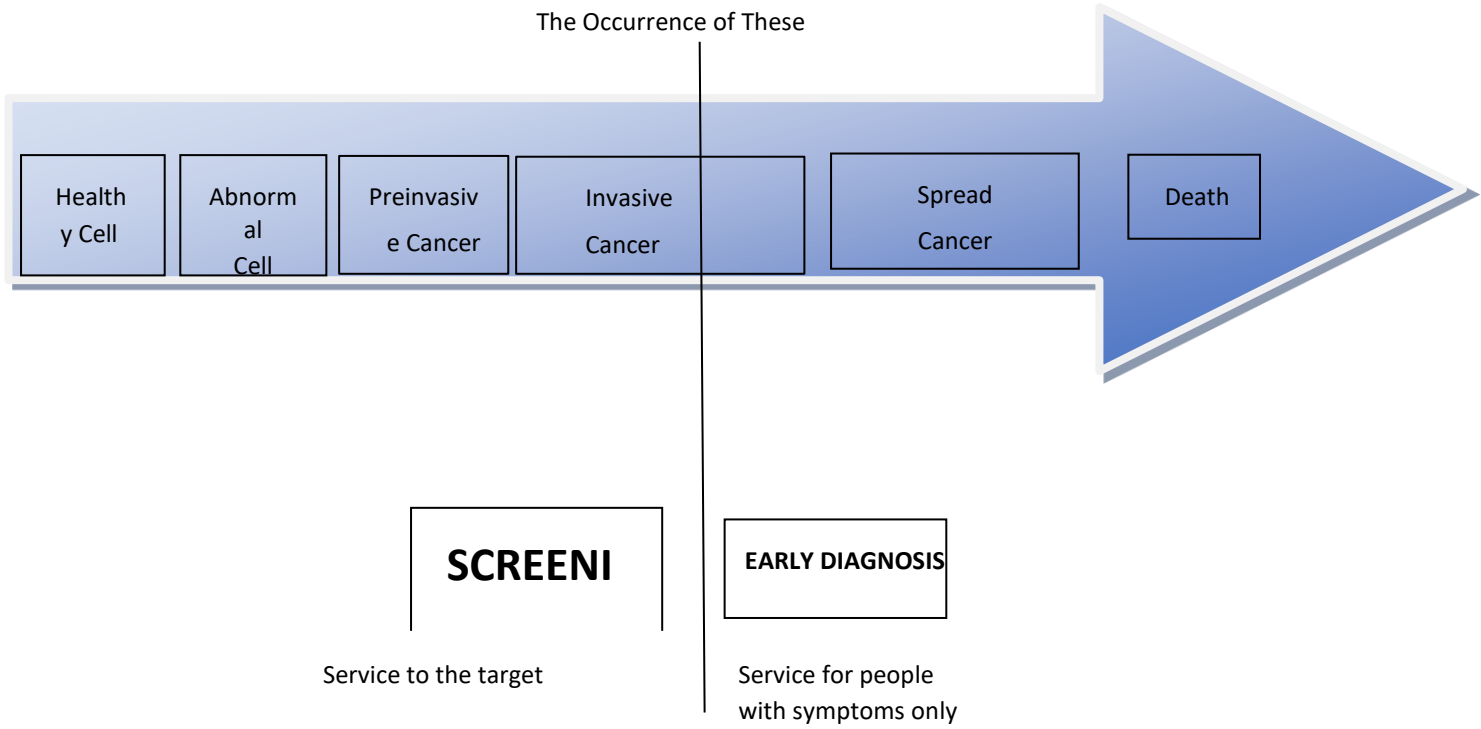


Figure 1. Chart of Disease Stages and Screening Time

RESOURCES

1. Wilson JM, Jungner G. The principles and practice of screening for disease. Geneva, Switzerland: World Health Organization; 1968. (Public Health Papers no. 34)

2. Andermann, A., Blancquaert, I., Beauchamp, S., & Déry, V. (2008). Revisiting Wilson and Jungner in the genomic age: a review of screening criteria over the past 40 years. *Bulletin of the World Health Organization*, *86*, 317-319.

3. Blamey, R. W., Wilson, A. R. M., & Patnick, J. (2000). Screening for breast cancer. *Bmj*, *321*(7262), 689-693.

4. Olsen, J., Saracci, R., & Trichopoulos, D. (Eds.). (2010). *Teaching epidemiology: A guide for teachers in epidemiology, public health and clinical medicine*. OUP Oxford.

5. World Health Organization. (2017). Guide to cancer early diagnosis.

6. World Health Organization. (2006). *Cancer control: knowledge into action: WHO guide for effective programmes* (Vol. 2). World Health Organization.

7. World Health Organization. (2002). *National cancer control programmes: policies and managerial guidelines*. World Health Organization.

4.1.2. Breast Cancer Screenings

General information

Breast cancer is the most common cancer and the most common cause of death in women in the world and in Turkey. According to the data of IARC (International Agency on Cancer for Research), affiliated to the World Health Organization (WHO), the number of newly diagnosed breast cancer patients worldwide in 2018 is 2,000,088, and the difference between lung cancer, which is the most common cancer, is only approx. 5,000 [1]. The incidence of breast cancer in Turkey is over 50/100,000, and the number of newly diagnosed patients in 2018 was calculated as 22,500 [1-2].

In a study published in 1994, the incidence of breast cancer in Turkey was determined as 24/100,000 [3]. The incidence of breast cancer has increased approximately 2.5 times over the past 25 years [1-2].

The reasons for this increase are:

1) Change in lifestyle (obesity, inactivity, not giving birth, late birth (>35 years), short-term lactation, early menarche, late menopause, long-term use of birth control pills and menopause treatment, etc.),

2) Population aging,

3) Increasing awareness (warnings from the media, information about breast cancer in breast and menopause polyclinics and referrals for screening mammography, increasing the knowledge and education level of women, etc.), increasing the number of irregular mammograms,

4) It can be listed as an increase in population.

This rapid increase in the frequency of breast cancer in our country requires a serious study for prevention, screening and early diagnosis.

Although the incidence of breast cancer is increasing in Turkey, most of the patients are diagnosed at an advanced stage. In our study, which was published this year and included 20,000 patients, when the pathological stage rates of patients diagnosed with breast cancer were examined; Stage 0 (Ductal carcinoma in situ) is 4.7%, Stage I 28.5%, Stage II 48.3%, Stage III 14.5%, and Stage IV 4% [2]. In developed countries, the rates of Stage 0 and I breast cancer are 20-25% and 50-60%, respectively. When these results are compared, we see that the diagnosis of breast cancer is made very late in our country. In our "Bahçeşehir Organized Community-Based Mammography Screening Project", which we completed last year in Bahçeşehir and lasted for 10 years, 13.5% of 130 patients diagnosed with breast cancer were diagnosed with Stage 0 and 57.9% with Stage I breast cancer. These results show how effective community-based mammographic screening, performed by invitation from home, is in providing early diagnosis, as in the Bahçeşehir Screening Project [4].

The results described above show that education and awareness of the target population is important for breast cancer prevention, screening, early diagnosis and effective treatment in our country. We can emphasize that the health system should create an infrastructure for education, awareness, prevention, screening, diagnosis and treatment, develop the existing infrastructure, expand the practices at the national level, and increase the number of health workers trained in this field.

RESOURCES

1. *Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68(6):394-424.*
2. *Ozmen V, Dogru V, Ozmen T. Breast cancer in Turkey: Analysis of 20.000 patients with breast cancer. Eur J Breast Health. 2019; 15:141-146.*
3. *Fidaner C, Eser SY, Parkin DM. Breast Cancer Incidence in Izmir in 1993-1994: first results from Izmir Cancer Registry. Eur J Cancer. 2001;37(1):83-92.*
4. *Ozmen V, Gurdal SO, Cabioglu, et al. Cost-Effectiveness of Breast Cancer Screening in Turkey, a Developing Country: Results from Bahçeşehir Mammography Screening Project. Eur J Breast Health 2017; 13(3):117-122.*

Screening in Breast Cancer

This section has been prepared in accordance with the Turkish Society of Radiology [TRD], Breast Screening Guide, the joint opinion published by EUSOBI and 30 National Breast Radiology Units, and the National Breast Cancer Screening Standards prepared by the Cancer Department of the Ministry of Health.

What is screening?

Screening is the detection of asymptomatic diseases with tests and examinations that can be applied quickly in a population. Cancer screening, on the other hand, is to detect any organ cancer before it causes a complaint and without symptoms (asymptomatic). In order for breast cancer screening to be successful, the method applied must be easily accepted by women, have few side effects, be easily applied, be free and economical. In addition, it is important to prolong the life expectancy and to protect the breast from which the cancer originates, with early diagnosis through screening. In order to screen, the disease should constitute an important health problem in the community, early diagnosis should provide an advantage in terms of treatment and reduce mortality [1].

Breast self-examination from the age of 20, annual clinical examination after the age of 20, and mammography after the age of 40 are recommended as screening methods in breast cancer (Figure 1-2). Clinical studies show that home-only mammographic screening reduces mortality due to breast cancer, while breast self-examination and clinical examination increase breast cancer awareness [2-3].

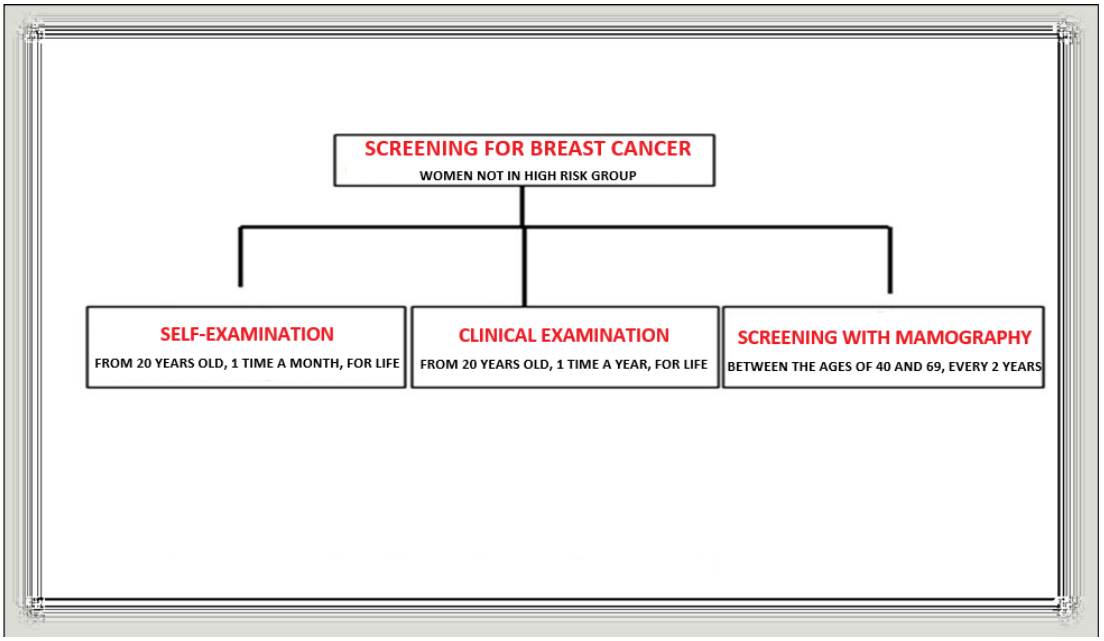


Figure 2. Screening Methods in Breast Cancer

Randomized controlled studies and population-based screening studies conducted in America, Europe and Canada have shown that MG reduces deaths from breast cancer by 20-40% [2]. For this reason, mammography is used as a screening method for breast cancer all over the world, and it is observed that early diagnosis of breast cancer is made in countries where this method is applied in a community-based and organized manner. While the contribution of screening in reducing mortality in breast cancer is 2/3, the effect of therapeutic methods is calculated as 1/3 [2-3]. In addition, with early diagnosis, treatment costs are reduced and treatment is less invasive. Screening reduces the number of metastatic axillary lymph nodes, resulting in fewer lymphatic dissections and reduced complications of lymphedema [4].

Screening guides and screening programs are different concepts. While preparing the screening guidelines, the aim is to organize scientific data for the benefit of the patient, regardless of whether the country's resources can fulfill the screening recommendations. Screening programs, on the other hand, are screening activities determined by the available resources in the main framework organized by the health system. The aim here is to scan by keeping the existing sources in the foreground without leaving the scientific data [5]. The overall results and quality of the scans depend on the performance of the screening process. For the implementation of the program, cost-effectiveness analysis, cooperation between institutions, technical training, standardization and quality assurance in screening centers are important for optimizing screening participation and screening performance. In order for the screening process to be effective, that is, to achieve the goal of "reducing deaths due to breast

cancer", more than seventy percent of the target population must have participated in the screening. For screening to be successful, quality assurance principles must be strictly followed at every stage [3-5].

Breast Self Examination (BSE)

We recommend our women to perform breast self-examination every month after the age of 20. During this examination, it is checked whether the images of both breasts are symmetrical by standing in front of the mirror (Picture 1). Nipple and skin collapse or recession, skin redness and edema are examined. With this examination, tumors close to the skin and nipples can be noticed by the woman herself at an early stage.

Most of the women are worried, thinking that they will not be able to notice a newly developing tumor in the breast themselves. However, a woman who examines herself regularly can distinguish a newly developing mass, a recession or discoloration of the breast skin or nipple, and an asymmetrical appearance. The masses that are suspicious of cancer are harder than other breast tissue (walnut-like), with indistinct borders, limited movement, and usually painless. A woman who notices a mass in her breast should consult her doctor immediately.

Breast self-examination should be done standing in front of the mirror and then lying down. While the hands are on the head in front of the mirror, the appearance of both breasts is checked in the mirror (Picture 2). The image of both breasts must be symmetrical. It is checked whether there is recession in the nipple, collapse in the breast skin or color change. Then, the hands are placed on the hips and pressed strongly, and by leaning forward, it is checked whether both breasts move freely on the chest wall. Breast examination is performed with the tips and inner parts of the 2nd, 3rd and 4th fingers of the hand (Picture 3). The nipples are squeezed lightly to check for discharge. At this time, the breast tissue is gently compressed between the breast skin and the chest wall, and it is checked whether there is a hard and painless tumor with irregular borders. While the right hand is behind the head, the tips and inner parts of the 2nd, 3rd and 4th fingers of the left hand and the left breast are examined by circling the left breast, while the left hand is on the head, the right breast is circled from top to bottom, from the bottom up, from the outside to the inside, and starting from the nipple to the outside (Picture 4). Then, the right and left armpits are examined by pressing lightly. Repeat the same steps by lying on your bed and placing a pillow under your

back (Picture 5).

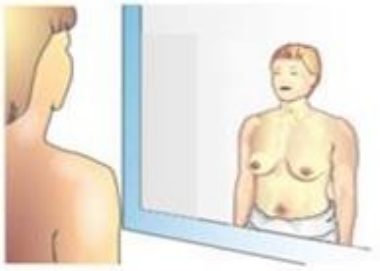


Image 1. Control of both breasts in front of the mirror

Image 2. Control of both breasts with hands behind the head

Image 3. Breast examination is done with the inner parts of the 2nd, 3rd and 4th fingers of the hand.

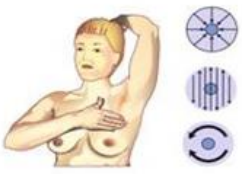


Image 4. With the left hand on the head, the right breast is examined by circling from top to bottom, from bottom to top, from outside to inside, and from the nipple to the outside. The right breast is examined in the same way.

Image 5. Breast examination is repeated while lying on the bed and placing a pillow under the back.

Clinical Breast Examination

Although breast cancer is usually seen after the age of 40, it can be seen less frequently between the ages of 20 and 40. Approximately 20% of patients diagnosed with breast cancer in
our country are under the age of 40. Therefore, breast examination by the doctor should be started at the age of 20 and should be continued once a year. These examination intervals that we have determined may be recommended differently by the doctor for women who have problems with their breasts or are in the high risk group.

Among the benign tumors of the breast, hard, smooth-limited slippery tumors, we call fibroadenoma, lead. They are most often seen in women between the ages of 20-35. They do not need to be removed unless they grow rapidly [>3 cm] and change shape.

The clinical examination can be performed by a general surgeon, family doctor or gynecologist. The examination starts by observing the symmetry and movements of the breasts in women standing. Then, the breasts and regional lymph nodes (axilla, mammaria interna and supraclavicular) are checked by sitting (Picture 6-8). Breast examination is done by lying down and placing a pillow under the back. Both breasts are examined by drawing a circle from top to bottom, bottom to top and starting from the nipple to the periphery (Picture 9). Since the breasts are very dense in women who are under the age of 35, have never given birth and have not breastfed, the doctor who performs the examination primarily prefers ultrasonography as the imaging method. He or she may then request mammography or magnetic resonance imaging.

Image 6. Clinical Breast Examination: The right breast is examined with the left hand.

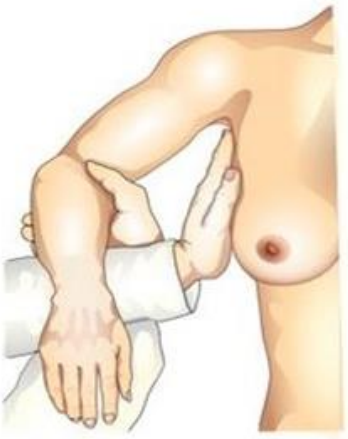


Image 7. Clinical Breast Examination: The right axilla is examined with the left hand.

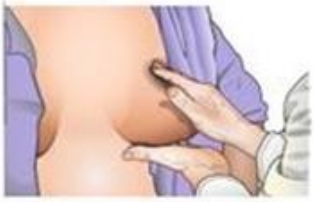


Image 8. Clinical Breast Examination: The left breast is examined while sitting down.

Image 9. The right breast is examined while lying down.

Screening with Mammography

Screening is performed for early diagnosis of breast cancer in women who do not have mammography complaints. During the scan, a standard film is taken for both breasts in two planes, one mediolateral oblique (MLO) and the other craniocaudal (CC). The European Imaging Society (EUSOBI) primarily recommends scanning with digital mammography (DMG) rather than traditional MG or phospho-plate computed radiography (CR). Digital MG is more sensitive than traditional MG, especially in women with dense fibroglandular tissue. Digital mammography is an examination similar to traditional MG. It involves capturing the image with an electronic detector and storing it in the computer. It has advantages such as high image quality, low radiation, image processing and archiving. Therefore, EUSOBI recommends that new imaging units be based on direct digital technology and can be updated [5].

With the digital mammography method used today, a clearer image is obtained by using a lower radiation dose [0.4mSv] and the diagnosis can be made when the disease is in the very early stages.

New technologies

Digital Breast Tomosynthesis (DMT) is a modification of digital mammography in the form of a mobile x-ray source and a digital detector. Multiple low-dose digital mammograms of the compressed breast are obtained while the X-ray source moves at reduced angles (15^0-5^00). Then, images with a thickness of 1 mm are combined by the computer to create a three-dimensional image. Superpositions are eliminated in dense breasts. In studies comparing tomosynthesis with DMG, an increase in cancer detection rate and a decrease in recall rate were found with tomosynthesis. Current data show that tomosynthesis reduces the false-positive rate and increases the cancer detection rate in dense breasts [4]. The updated NCCN guideline recommends considering annual tomosynthesis screening starting at age 40 in a woman at average risk for breast cancer [6].

Contrast-enhanced mammography, after intravenous contrast material administration, breast imaging is performed with DM or DMT. In recent meta-analyses, although its sensitivity is high (98%), its specificity is low (38%), and it is not recommended for screening [5].

Women to Participate in Screening

Based on randomized controlled studies, the International Agency for Research on Cancer (IARC) stated that mortality was reduced by 40% with screening MG in the age range of 50-69 years, the rate of false positive biopsy was <1%, and the rate of *overdiagnosis* in 20 years of screening was between 1 and 10%. Based on cohort and case-control studies between the ages of 40-49 and 70-74, it is said that mortality decreases more limitedly. There is insufficient evidence in articles supporting mammographic screening for these age groups. The IARC recommended screening with MG every two years as primary priority for women aged 50-69 years, secondary priority screening up to the age of 73 or 75 years, and annual and third priority screening for women aged 40-49 years. This decision varies from country to country. Mammographic screening should be terminated if the life expectancy of the woman is less than 5 years. Generally, this age is determined as 70-74 years [6].

According to the Screening Guide published by the Turkish Society of Radiology, TRD Qualification Board, Guidelines and Standards Committee [4], the starting age of MG screening is accepted as 40 years old. If women are not in the high-risk group, screening mammography should begin at age 40. Screening can be started earlier in women who are in the high-risk group. Patients who are symptomatic or with pathology in previous examinations should be followed up at short intervals, and other methods should be used when necessary.

In studies conducted in our country, unlike western countries, approximately half of the patients diagnosed with breast cancer in Turkey are under the age of 50, so the Ministry of Health recommends that mammographic screening be started at the age of 40 and performed every 2 years [6-8].

In summary, according to the National Screening Guidelines, Screening mammography should be performed every two years in women >40 years of age and asymptomatic. However, women in the high risk group [genetic carrier, family history, dense breast structure, etc.] should be screened at an earlier age, at recommended intervals and with recommended screening methods. Asymptomatic women with prophylactic or cosmetic breast implants should also be included in the screening program.

Screening Program in Turkey in 2004, national standards for breast cancer screening in women were published by the Ministry of Health's Cancer Control Department, similar to

the European Union Countries, and it is recommended that mammographic screening be done every 2 years between the ages of 50-69. However, in Turkey, **unlike European countries, it has been determined that the population is young and** approximately half of the breast cancer cases are under the age of 50 and in the premenopausal period. For this reason, the standards to be followed during the community-based breast cancer screening program studies were rearranged by the Ministry of Health Public Health Institution in 2012. According to the '**National Standards of the Breast Cancer Screening Program**', it is recommended to start screening at the age of 40 in women who are not in the high-risk group, and to perform the screening every 2 years between the ages of 40-69 [6].

The fact that the population structure in Turkey is young in clinical and prospective studies, that approximately half of the patients diagnosed with breast cancer are under the age of 50 and premenopausal, and that 40% of the women screened in the Bahçeşehir Mammography Screening Program are between the ages of 40-49 are factors in this decision [7,8].

Ultrasonography in Scanning

Ultrasonography (US) has been used since the 1980s to supplement screening mammography. Compared with screening MG alone, the addition of US, increased the rate of cancer detection, as well as recall and unnecessary biopsy rates, especially in women with dense breast tissue with low MG sensitivity. US is not preferred in routine screening because of its low specificity and increased cost when added to the screening program [5].

MRI in Scan

It is used as an additional screening method to mammography and ultrasonography in high-risk women, despite its disadvantages such as being an invasive and expensive method, not being widely performed and not having enough specialists to evaluate it. Centers that will screen for breast cancer with MRI should have the equipment to perform MRI-guided biopsy. Turkish Society of Radiology (TRD) states that the guide prepared by the American College of Surgeons (ACS) for the screening of breast cancer with MRI in high-risk patients is also valid for our country. In addition, another important feature of this guide is to prevent abuses by determining the subgroup that should not undergo MRI for screening [5].

Screening in High-Risk Women

In developed countries, women who are not in the risk group have a 12% chance of developing breast cancer. Although this rate is lower in our country and other developing countries, it is increasing gradually. The probability of being diagnosed with breast cancer in women with several of the risk factors for breast cancer is 3-4 times higher than in the normal population. Numerous models have been developed to identify high-risk women [figure 2]. Here, taking into account the presence of breast cancer in the family, age at menarche, age at first birth, age at menopause, body mass index, presence of breast biopsy, presence of Atypical Lobular Hyperplasia (ALH), Atypical Ductal Hyperplasia (ADH) and lobular carcinoma in situ (LCIS), BRCA1/2 and other pathogen gene positivity, the lifetime, 5- and 10-year risk of breast cancer is calculated when women live to 85 years [9].

Women at high risk for breast cancer should be screened at an earlier age with MG and/or MRI and US. In studies investigating the efficacy of US and MRI in addition to MG in high-risk women, MRI was found to be the method with the highest sensitivity and selectivity despite its high cost [5]. In this study, the sensitivity of MRI is between 77-100%, the sensitivity of MG is between 13-40%, and the sensitivity of US is between 13-33% [6].

Screening in the high-risk group;

1. It should be started 10 years before the age at which the first-degree relative has breast cancer.
2. After the diagnosis of breast cancer, screening should be continued at any age.
3. In cases undergoing breast-conserving surgery, the first imaging should be performed 12 months after radiotherapy. During the first 2 years, if desired, imaging can be performed every 6 months, then annual imaging is started.
4. Those who have lobular intraepithelial neoplasia or atypical ductal hyperplasia as a result of breast biopsy performed for any reason are kept under close follow-up.
5. In the group with known or suspected BRCA1 gene mutation carriers, screening is started as early as possible, usually at the age of 20. Likewise, screening starts between the ages of 25-30 in those who are carriers of the BRCA2 gene mutation.
6. In those receiving radiotherapy to the thorax, screening is started after 8 years or when the patient reaches 25 years of age.

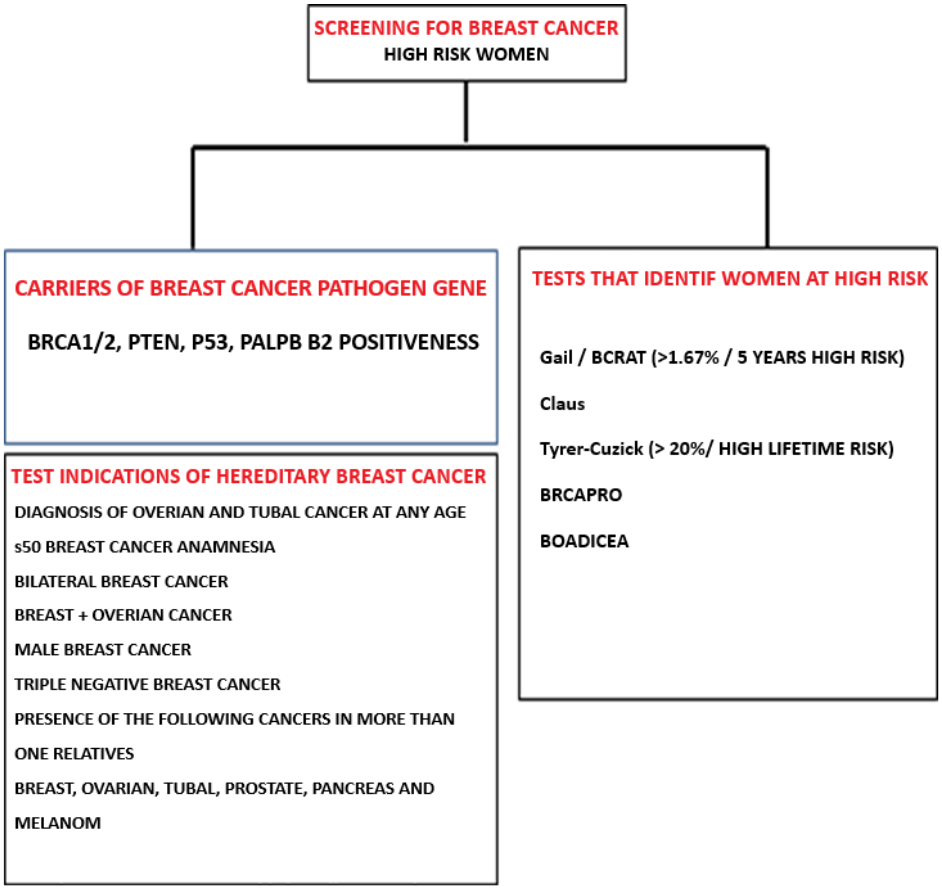


Figure 3. Screening of High Risk Group for Breast Cancer

Joint Decision Making with Women to Scan

For early diagnosis of breast cancer, women's education, awareness should be increased and a regular screening program should be implemented by invitation from home. Breast cancer risk

Age is the most important factor in decision making in low-risk women below 15%. Since the incidence of breast cancer is low in women under the age of 40 and the diagnostic sensitivity of mammography is limited, screening is not recommended for them, while it is recommended that screening be applied individually for those aged 40-49 years.

In low-risk women, screening should be done with MG, and USG or MRI should be used when necessary. Screening mammography is recommended at 2-year intervals. Clinical breast examination and breast self-exam are important to increase awareness as part of screening.

In women with a first-degree relative with breast cancer and no genetic mutation, screening is similar to low-risk women. Breast cancer in first degree relative In the premenopausal period, although there are those who recommend starting screening at a younger age, there are no studies showing that this approach contributes to reducing mortality. While determining the screening program of the woman, the possible benefits and

harms should be explained to her and a personalized screening strategy should be created. Negative discussions about mammographic screening continue today. Besides the radiation risk of MG, it is mentioned that it causes false negative and false positive results, unnecessary diagnostic procedures and unnecessary treatments. It is stated that the decrease in deaths from breast cancer is related to new treatment methods as well as early diagnosis by mammography [10]. However, we should not forget that mammography performed by invitation from home catches asymptomatic breast cancer, reduces deaths, the radiation dose given is very low, mammography performed with digital mammography in an experienced screening center and evaluated by an experienced specialist is the only accepted method for breast cancer screening today.

In summary, **mammography is a basic method for screening and has no alternative.** Ultrasonography and MRI are used as additional methods to illuminate a lesion detected in scanning mammography.

Duties of KETEM doctor and nurse in screening:

Training and examination of women who apply to KETEM for breast cancer, screening, breast self-examination, identifying women in the breast cancer risk group and directing them to screening are important duties. Women who come for screening should be invited for mammography regularly every 2 years, unless their experts suggest otherwise. It is necessary to evaluate and inform the mammograms in the radiology center [3]. In addition, it is important to direct the suspects with positive screening results to the diagnosis center and to follow up.

Duties of Family Physicians in Screening:

Training the women in the population they are responsible for on screening programs according to their age groups, training for breast cancer and breast self-examination, getting them examined, identifying the women in the breast cancer risk group, directing them to screening, and directing and following up the ones with positive screening results to the diagnosis center are important duties. The women whom they thought pathology as a result of the examination They should refer them to secondary care institutions [3].

RESOURCES

1. *Wilson JMG, Jungner G. Principles and practice of screening for disease. Geneva: WHO; 1968.*
2. *Bethany L. Niell, Phoebe E. Freer, Robert Jared Weinfurtner, et al, Screening for Breast Cancer Radiol Clin N Am 2017, 55: 1145–1162.*
3. *Özmen V, Fidaner C, Aksaz E, et al. Türkiye'de Meme Kanseri Erken Tanı ve Tarama Programların Hazırlanması "Sağlık Bakanlığı meme kanseri erken tanı ve tarama alt kurulu raporu", Journal of Breast Health 2009, 5(3):125-134.*
4. *Seely JM, Alhassan T. Screening for breast cancer in 2018-what should we be doing today? Curr Oncol 2018; 25(1): 115-124.*
5. *Meme Kanseri Tarama Rehberi; Türk Radyoloji Derneği, TRD Yeterlilik Kurulu, Rehberler ve Standartlar Komitesi, 2011.*
6. *https://www.turkrad.org.tr/assets/2017/Meme-kanseri-taramasi-gorus.docx Access date: 15 December 2019*
7. *https://hsgm.saglik.gov.tr/tr/kanser-tarama-standartlari/listesi/meme-kanseri-tarama-programı-ulusal-standartları.html Access date: 15 December 2019.*
8. *Cantürk NZ, Çakmak GK, Meme Kanserinde Tarama http://www.tmhdf.org.tr/Uploads/Editor/bolum_22_converted.pdf. Date accessed: April 6, 2020.*

Bahçeşehir Breast Cancer Population-Based Screening Program

The community-based organized mammographic screening program was first implemented in New York with the Health Insurance Plan (HIP) launched in 1963, and is now being implemented in all developed countries at different screening intervals and in different screening age ranges [1]. As a first in our country, a 10-year mammographic screening program was carried out regularly by the Breast Health Association (MEMEDER) by invitation from home. The reasons why such a program cannot be implemented in developing countries can be listed as the inability to establish the necessary infrastructure for mammographic screening, the lack of trained health workers and radiology specialists, and social, economic and cultural reasons [2]. In fact, the inadequacy of scientific studies on this subject, not knowing how often the screening can be done in which age group, and lack of cost-effectiveness analysis are also important shortcomings. Today, mammographic screening, which is generally applied in our country, is performed as a result of women being invited by the media, family physicians, and sometimes by the system. Women in the 40-69 age group who apply to the Ministry of Health Cancer Early Diagnosis Screening and

Training Centers (KETEM), University Medical Faculties Polyclinics, Public Hospitals Breast Polyclinics, Private Hospitals and Oncology Institutes are asked to have a mammogram. With a legal regulation made by the Ministry of Health, screening mammography is taken free of charge. In addition, in an application initiated by the Cancer Department of the Ministry of Health in recent years, women of screening age are invited to the screening by visiting the neighborhoods with mobile screening systems, the films obtained are evaluated by a central system and the suspicious screening results are reported to the women [3].

In order to demonstrate the feasibility of a community-based, organized, continuous and invitation-based screening program within the social, cultural, educational and economic structure of our country, the "Bahçeşehir Community-Based Mammographic Screening Project", which would last for 10 years (2009-2019), has been carried out successfully [4-9]. The other aims of this study, which will set an example for low-middle-income countries, are to determine the age of screening in our country (40 or 50), to increase the rates of survival and breast-conserving surgery by increasing the rates of in situ ductal and early invasive breast cancer, and to reveal whether the mammographic screening program we apply is cost effective or not according to the conditions in our country. Before starting the screening, a special software program was prepared and approximately 20,000 houses in Bahçeşehir and its surrounding 4 neighborhoods were visited and the women eligible for screening were recorded. The women who were invited to our screening center were examined by a breast surgeon and two-way digital mammograms were taken. These films were evaluated by two independent breast radiologists. Ultrasonography was performed in our center in suspicious cases. Cases thought to be malignant were referred for biopsy. The cases diagnosed with breast cancer were referred for treatment and followed up. Screening participation rates were around 85%.

During the ten-year screening period (2009-2019), 8,823 women aged between 40 and 69 were included in the screening program. A total of 27,754 screenings were performed, and breast cancer was detected in 130 women. 51 (39.2%) of the patients were between the ages of 40-49 and 79 (60.8%) were between the ages of 50-69. The average age of the patients was 53.3±7.8 years. 17 (13.1%) of these were ductal carcinoma in situ (DCIS), and 113 (86.9%) were invasive cancers. The rate of DCIS in the younger age group (40-49 years) was close to twice that of the older age group. Breast conserving surgery was performed in

81% of the patients, and pathological Stages 0 and I were found in 60% of the patients. When these results obtained from the Turkish Breast Diseases Associations, where 20,000 patients were analyzed, are compared with the results in the Turkish Federation (TMHDF) registry program, we can see that the rates of breast conserving surgery and early stage (Stage 0, I) breast cancer have doubled as a result of this screening program. The 10-year survival rate of patients diagnosed in the screening program is 96.9%, it is 76% for symptomatic patients in the registry program.

High participation in the Bahçeşehir Mammographic Screening Program and high rates of early-stage breast cancer (DCIS and Stage I) show that population-based screening can be applied and early diagnosis can be achieved in our country as well. When the life expectancy of patients diagnosed with breast cancer through screening is compared with those in the breast cancer registry program, it is revealed that screening prolongs the life expectancy by an average of 5.84 years [10].

A cost-effectiveness analysis of the Bahçeşehir screening program was also performed [10]. In this analysis, the expenditures for the screening and treatment of patients diagnosed with breast cancer by screening (asymptomatic) were compared with the expenditures for the treatment of patients who were enrolled in the TMHDF breast cancer registry program and who were not screened (symptomatic patients). The number of women participating in the third screening period is 7167, and the number of asymptomatic patients diagnosed with breast cancer is 67. The pathological stages of these patients (from Stage 0 to Stage IV, respectively) are 19.4%, 50.7%, 20.9%, 7.5% and 1.5%. In other words, in the Bahçeşehir screening program, 1/5 of the patients are in stage 0 and half of them are in stage II, and it shows parallelism with the stages of patients screened in developed countries. The stages of symptomatic breast cancer patients included in the TMHDF Breast Cancer Registry Program are 4.9%, 26.6%, 44.9%, 20.8%, and 2.8%, respectively, from Stage 0 to Stage IV. In other words, the in situ cancer rate of asymptomatic patients participating in the screening program is 4 times higher and the rate of Stage I breast cancer is 2 times higher. The increased cost-effectiveness ratio (The Incremental Cost-Effectiveness Ratio (ICER)) was calculated as the excess money spent in the Bahçeşehir Screening Program (BTP) for 1 year more life expectancy compared to the Federation's Registration Program (FKP) [ICER=Cost (BTP)–Cost (CAP) / Life expectancy (LTP) – Life expectancy (FRP)]. In Turkey, the per capita income in 2014 is 10,650 dollars. (Gross Domestic Product=USD 10,650 for GDP 2014).

According to the World Health Organization, an ICER value below GDP is considered cost-effective. In our study, ICER was calculated as 1,897 USD/year, which is 15% of the annual per capita income. In other words, the Bahçeşehir screening program extends the life expectancy of patients diagnosed with breast cancer up to 6 years compared to patients with breast cancer who do not participate in the screening, and it is cost effective.

A recent study has been published showing that mammographic screening performed by invitation from home significantly reduces mortality due to breast cancer and evaluating all studies in the literature [10]. In this study, which systematically examined 60 well-designed clinical studies, mortality in women invited for mammographic screening decreased by 33-43% in Northern Europe, 43-45% in Southern Europe, and 12-58% in Western Europe. The difference between invited and non-invited ranges from 4% to 31% [11].

RESOURCES

1. *Shapiro S, Venet W, Strax P, et al. Ten- to fourteen-year effect of screening on breast cancer mortality. J Natl Cancer Inst 1982; 69:349e55.*
2. *2.Ozmen T, Soran A, Ozmen V. Comparison of Barriers Against Mammography Screening in Socio-economically Very Low and Very High Populations. Cureus. 2016 Jul 14;8[7]: e690.*
3. *T.R. Ministry of Health Cancer Statistics http://hsgm.saglik.gov.tr/tr/kanser-istatistikleri*
4. *Ozmen V, Ozaydin NA, Cabioglu N, et al. Survey on a mammographic screening program in Istanbul, Turkey. Breast J. 2011 May-Jun;17[3]:260-7. doi: 10.1111/j.1524-4741.2011.01065.x.*
5. *Kayhan A, Gurdal SO, Ozaydin N, et al. Successful first round results of a Turkish breast cancer screening program with mammography in Bahcesehir, istanbul. Asian Pac J Cancer Prev. 2014;15[4]:1693-7.*
6. *.Ozmen V, Cabioglu N, Gürdal SO, et al. Bahcesehir Mammography Screening Project [BMSP] is cost effective in a developing country. San Antonio Breast Cancer Symposium 2015, 8-12 December, 2015.*
7. *Kayhan A, Aribal E, Sahin C, et al. Radiologic findings of screen-detected cancers in an organized population-based screening mammography program in Turkey. Diagn Interv Radiol. 2016; 22[6]:508-513.*
8. *Ozmen V, Boylu S, Ok E, et al. Factors affecting breast cancer treatment delay in Turkey: a study from Turkish Federation of Breast Diseases Societies. Eur J Public Health. 2015;25[1]:9-14.*

9. *Ozmen V. Controversies on Mammography Screening in the World and Bahceşehir Population-Based Organized Mammography Screening Project in Turkey. J Breast Health. 2015 Oct 1;11[4]:152-154.*
10. *Ozmen V. Controversies on Mammography Screening in the World and Bahceşehir Population-Based Organized Mammography Screening Project in Turkey. J Breast Health. 2015 Oct 1;11[4]:152-154.*
11. *.Zielonke N, Gini A, Jansen EEL, et al. EAM; EU-TOPIA consortium. Evidence for reducing cancer-specific mortality due to screening for breast cancer in Europe: A systematic review. Eur J Cancer. 2020 Mar; 127:191-206. doi: 10.1016/j.ejca.2019.12.010. Epub 2020 Jan 10. PMID: 31932175.*

Breast Cancer in Turkey "Demographic, clinical, pathological and survival analysis of 20.000 Patients"

Breast cancer is the most common cancer and the most common cause of death among women in Turkey. Demographic, clinical and pathological characteristics of 13.000 patients treated with the diagnosis of breast cancer in our country were included in our previous book [1]. In this book, the demographic, clinical, pathological characteristics and survival data of our patients who were diagnosed with breast cancer, whose number reached 20,000, between May 1, 2005, and April 17, 2015, when we started the registration program, were analyzed [2]. In addition to the previous book, patients diagnosed with male breast cancer and ductal carcinoma in situ (DCIS) were also analyzed.

576 parameters under 242 different titles were evaluated in the National Breast Cancer Database (UMKVT) of the Turkish Federation of Breast Diseases Associations (TMHDF). 98.9% of breast cancer patients recorded in a period of approximately 10 years are female and 1.1% are male. Invasive breast cancer was diagnosed in 19,201 patients, and DCIS was diagnosed in 576 patients. The number of male breast cancer patients is 223.

The mean age of women diagnosed with breast cancer at the time of diagnosis is 51.8 (±12.6, range 14-97), of which 16.4% are under the age of 40 and 37.2% are premenopausal. The mean age at diagnosis is 57.32 (±14.076, 24- 87) in male breast cancer patients, and 51.12 (±11.69, 18-89) in patients with DCIS. Considering the age-adjusted frequency curve at the time of diagnosis in female patients diagnosed with invasive breast cancer, the incidence of cancer reached a maximum level of 16.6% in the 45-49 age group, and then decreased to 7.3% in the 65-69 age group. It is seen that it decreases, and then rises again.

Although the risk of developing breast cancer in male patients decreases in the 55-60 age range, it increases with increasing age.

DCIS was found in 5% of female patients and invasive breast cancer was found in 95% of female patients. 86% of invasive breast cancers have invasive ductal, 11.9% have invasive lobular or mixed cancer (invasive ductal+invasive lobular cancer) histological type. Histology
is grade III in 45.4% of these patients. Considering the pathological stages of all breast cancer cases, Stage 0 is 4.7%, Stage I is 28.5%, Stage II is 48.3%, Stage III is 14.5%, and Stage IV is 4%. The mean tumor diameter is 25.2 mm (SD ±17.3; range 0-250 mm). 47.2% of women with invasive breast cancer have pN0, 52.8% have pN1-3. Of these, 72.6% are positive for estrogen receptor (ER), 62.7% for progesterone receptor (PR), and 21.8% for HER-2 receptor. When the molecular subtype analyzes of the cases were performed, luminal A was found at a rate of 30.4%; 50.3% of them were luminal B (Ki67>14%, HG=3),

11.2% were triple negative and 8.1% were HER-2 positive.

In women with invasive breast cancer, the mean age at menarche is 13.4 years, breastfeeding duration is 24 months, miscarriage rate is 19%, frequency of abortion is 30%, history of oral contraceptive use is 14.7%, and delivery rate is 86.4% (mean number of births 2.8). When surgical interventions were examined, 52% had modified radical mastectomy (MRM), 39% had breast-conserving surgery (BCS), 8% had simple mastectomy, and the remaining few patients had radical mastectomy (43 patients), subcutaneous mastectomy (11 patients) or only axillary dissection (16 patients) surgeries were performed. The mean follow-up period in these patients was 4.3 years, and the 5-year survival rate was calculated as 86%.

There are 575 patients with DCIS in the patient registry program. 14% of these were <40 years old, 87% had given birth and 32% had abortions. The rate of pre-menopausal patients is 43%, the rate of those who breastfeed for more than 12 months is 63%, the rate of those using oral contraceptives is 17%, and the rate of those using HRT is 12%. DCIS diameter is ≤2cm in 70% of patients and over 5cm in 8% of patients. ER and PR positivity rates are 75% and 66%, respectively. Mastectomy was performed in 32% of the patients and BCS was performed in 68% of the patients. The local recurrence rate is 3% during the 10-year follow-up period, and local recurrences are in the form of invasive cancer.

A total of 225 male breast cancer cases were included in UMKVT. The mean age of these patients was 57.8 (24-87), of which 11.3% were <40 years and 48% were >60 years. The rates according to the stages at the time of diagnosis: Stage I 23%, Stage II 50%, Stage III 16% and Stage IV 11%. Tumor diameter is ≤2 cm in 31% of patients. The distribution of histological grades is as follows; HG I 10.3%, HG II
51.7% and HG III 37.9%. The rate of HG II+III is 89.6%. Mastectomy was performed in all of these patients.

When the histopathological tumor types of male patients diagnosed with breast cancer are examined, 81% are invasive ductal cancer (IDC), 1% are ductal carcinoma in situ (DCIS), 1% are invasive lobular cancer (ILC), 1% are invasive mixed cancer (IMC) and 16% are other histopathological types. Lymphatic involvement is 50% in pN0, 34.8% in pN1, 6.5% in pN2 and 8.7% in pN3. Estrogen receptor (ER) is positive in 87.2% of the patients, progesterone receptor (PR) in 73.9%, and HER-2 receptor in 27%. In the analysis of 20,000 patients in UMKVT, the mean follow-up was 4.3 years, with a 5-year survival rate of 86%.

The number of patients followed up regularly in Istanbul Florence Nightingale Breast Center is 2124, of which 2032 (96.26%) have been treated with the diagnosis of invasive breast cancer and 122 (5.74%) with ductal carcinoma in situ (DCIS). Mean age at diagnosis of patients diagnosed with invasive breast cancer was 51.4±12.98, age at menopause 48.98±4.54, age at first menstrual period 13.10±1.64, age at first birth 19.81±11.49, number of births 1.69±1.34, and duration of lactation 17.17±21,13 months. 49.6% of the patients were premenopausal, 20.5% had a positive family history, and 1.5% had bilateral breast cancer. Clinical stages at diagnosis: 0.9% DCIS,
68.7% Stage I, 19.5% Stage II, 1.4% Stage III and 9.5% Stage IV breast cancer. Pathological stages from Stage 0 to Stage IV are 0.7%, 63.6%, 21.7%, 8.6%, and 5.3%.

The mean tumor diameter of patients diagnosed with invasive breast cancer is 24.80 ± 16.42 mm, the distance from the surgical margin is 10.39 ± 22.74 mm in patients with BCS, the number of SLNBs removed is 1.99 ± 2.11, and the number of lymph nodes removed in patients with axillary dissection is 14.76 ± 8 .32. The tumor is multifocal in 16.8% of patients and multicentric in 1.4%. The mean number of positive lymph nodes in patients with positive axilla was 3.07 ± 5.46. Among these patients, the rate of Ki 67 >14% was 62.7%,

and the rate of Ki 67 >20% was 54.2%. Lymphovascular invasion positivity was 59%, and sentinel lymph node biopsy was performed in patients with clinically negative axilla (69.4%). The rate of patients who underwent axillary lymph node dissection (ALND) is 55.3%. Estrogen (ER), progesterone (PR) and HER-2 receptors positivity, respectively: %76,9, %65,8 and %21,8.

After oncoplastic breast surgery was started in 2010 at Istanbul Florence Nightingale Breast Center, the rate of breast-conserving surgery (BCS) increased from 66% to 82.5%, and the rate of mastectomy decreased from 33% to 17.5% [1]. In particular, the application of the mini latissimus dorsi flap increased the chance of protecting the breast. In the median 70-month follow-up of 1400 patients who underwent BCS, local recurrence was observed in 53 patients (3.8%), and 41.5% of the patients with relapse were under the age of 40. True recurrence (around the primary tumor cavity) rate
is 62.3%, and the 5-year overall survival in these patients is 74.7%. The 5-year survival rate in patients with new primary tumors is 95% ($p<0.033$). In multivariate analysis, younger age (<40 years), tumor diameter (>20mm), high histological grade (HG 3), triple negative molecular subtype, and true recurrence were associated with overall survival.

In a multicenter prospective clinical study conducted by this center, the Oncotype DX score was found in the low-risk group in 56% of patients diagnosed with early-stage breast cancer (pT1-3 N0-mic M0) and showed that 21-gene analysis changed the systemic treatment decision in 31% of patients.

In this Breast Health Center, 5-year overall survival is 93.5%, 10-year overall survival is 86.6%, and 20-year overall survival is 77.3%. Overall 10-year survival rates by molecular subtypes were 88.2% in Luminal A, 89.3% in Luminal B, 79.4% in HER-2 positive group not receiving trastuzumab, 90.7% in HER-2 positive group receiving trastuzumab, triplet in the negative group (TNG), it is 74.9%.

RESOURCES

1. *Özmen V. Breast Cancer in Turkey: Clinical and Histopathological Characteristics (Analysis of 13.240 Patients). J Breast Health. 2014 Apr 1;10(2):98-105.*

2. *Özmen V, Özmen T, Doğru V. Breast cancer in Turkey: Analysis of 20.000 patients with breast cancer. Eur J Breast Health. 2019 Jul 1;15(3):141-146.*

Breast Cancer Risk Factors

Being a woman is the most important risk factor for breast cancer. Apart from this, advanced age (>50 years), early menarche (<12 years), late menopause (>55 years), never giving birth and not breastfeeding, giving birth at an advanced age (>35 years), radiotherapy applied to the thoracic region in childhood, long-term (>10 years) oral contraceptives and menopausal hormone replacement therapy (>5 years), chronic alcohol use, post-menopausal obesity, benign proliferative breast diseases, presence of atypical hyperplasia or lobular carcinoma in situ as a result of previous biopsy, dense breast on mammography structure, familial and genetic factors increase the risk of breast cancer. The most important genetic risk factors are BRCA 1 and BRCA 2 mutations. Diagnosis before the age of 40, presence of breast cancer or breast cancer-related mutations in the individual or close relatives, breast cancer in two first-degree relatives and men, history of ovarian cancer with breast cancer, presence of triple negative breast cancer, presence of a known cancer syndrome such as LiFraumeni/Cowden/Peutz Jeghers should suggest hereditary breast cancer [1– 9].

The risk models used to calculate the risk of breast cancer in women can be examined in three groups: 1. Programs that calculate the general breast cancer risk, 2. Programs that calculate the genetic risk of breast cancer in the individual, and 3. Programs that evaluate the risk for both.

Benefits of using risk models;

1. Reducing or eliminating risk
2. Early diagnosis
3. Reducing mortality
4. Providing accurate information for women and their doctors
5. Ability to assess individual breast cancer risk
6. Being able to direct high-risk individuals to advanced diagnostic methods (genetic examination)
7. Ability to determine individual radiological follow-up criteria
8. Ensuring the use of risk-reducing drugs
9. Planning of risk-reducing surgeries [10-14].

The most commonly used risk models in breast cancer can be listed as Gail, Claus, BRCAPRO and Tyrer-Cuzick. Different risk factors are questioned in these models. The Gail model mostly evaluates risk based on non-genetic, reproductive risk factors [10-14]. In the Gail model, only first-degree relatives are questioned for breast cancer, while in the Claus model, second-degree relatives are questioned. In the Gail risk model, the patient's age, racial characteristics, breast biopsy history and number, presence of atypical hyperplasia in breast biopsy, age at first menstruation, age at first live birth, and history of breast cancer in first-degree relatives are questioned.

The diagnostic performance of the Gail model has been demonstrated by many clinical studies. However, this model cannot be used in the following situations;

1. Women under 35
2. Those with a history of breast cancer
3. Patients with a diagnosis of lobular carcinoma in situ
4. Patients with a diagnosis of ductal carcinoma in situ
5. Those with a mutation in a known high-risk gene such as BRCA1 or BRCA2
6. Those with a history of cancer in relatives other than first degree
7. Those with a history of cancer on the father's side

The Gail model may not be a good model for individuals thought to be genetically inherited. According to the Gail model, if the 5-year breast cancer risk is $\geq 1.67\%$, the woman is in the high-risk group. In high-risk individuals, close follow-up, chemoprevention with tamoxifen, or prophylactic mastectomy can be offered to the patient [10-14].

The Claus model is more of a test to detect familial breast cancer. In Claus model;

1. Age of the person
2. Number of first- and second-degree relatives with breast cancer
3. The age in which first and second degree relatives with breast cancer had breast cancer is questioned.

In the Claus model, the biopsy result (atypical ductal hyperplasia), first menarche and age at first birth are not taken into account. Therefore, this model can only be used in patients with a family history of cancer [10-14].

The fact that more studies have been done in the clinic and it is easy to calculate,

causes the Gail model to be used more frequently. However, the Claus model is found to be more appropriate for women aged 29-35 with a family history of breast cancer [10-14].

The Gail and Claus models may not be helpful in calculating the risk of individuals with a family history of hereditary breast cancer [10-14]. BRCAPRO and Tyrer-Cuzick Risk Models are more preferred in women who are thought to have hereditary breast cancer.

While BRCAPRO frequently investigates the risk of BRCA1/2 gene mutation, risk factors other than BRCA1/2 are also questioned in Tyrer-Cuzick. Apart from close radiological follow-up, in cases whose genetic mutation is determined by testing, preventive mastectomies can also be considered. [14].

Currently, some of the known risk factors are not included in risk models. In particular, factors such as mammographic density, obesity, and serum steroid hormone measurements have not yet been included in the models [10-14]. It will be possible to make a more accurate risk estimation by modeling genetic data together with known risk factors.

RESOURCES

1. *Ban KA, Godellas CV. Epidemiology of breast cancer. Surg Oncol Clin N Am. 2014 Jul;23(3):409-22*
2. *Tryggvadóttir L, Tulinius H, Eyfjord JE, Sigurvinsson T. Breastfeeding and reduced risk of breast cancer in an Icelandic cohort study. Am J Epidemiol. 2001 Jul 1;154(1):37-42*
3. *Kelsey JL, Berkowitz GS. Breast cancer epidemiology. Cancer Res. 1988 Oct 15;48(20):5615-23*
4. *Collaborative Group on Hormonal Factors in Breast Cancer. Menarche, menopause, and breast cancer risk: individual participant meta-analysis, including 118 964 women with breast cancer from 117 epidemiological studies. Lancet Oncol. 2012 Nov;13(11):1141-51*
5. *Nelson HD, Zakher B, Cantor A et al. Risk factors for breast cancer for women aged 40 to 49 years: a systematic review and meta-analysis. Ann Intern Med. 2012 May 1;156(9):635- 48.*
6. *Yaghjyan L, Colditz GA, Collins LC et al. Mammographic breast density and subsequent risk of breast cancer in postmenopausal women according to tumor characteristics. J Natl Cancer Inst. 2011 Aug 3;103(15):1179-89*
7. *Feigelson HS, Jonas CR, Teras LR, et al. Weight gain, body mass index, hormone replacement therapy, and postmenopausal breast cancer in a large prospective study. Cancer Epidemiol Biomarkers Prev. 2004 Feb;13(2):220-4.*
8. *Henderson TO, Amsterda A, Bhatia S et al. Systematic review: surveillance for breast cancer*

in women treated with chest radiation for childhood, adolescent, or young adult cancer. Ann Intern Med. 2010 Apr 6;152(7):444-55; W144-54

9. *Eliassen AH, Colditz GA, Rosner B, et al. Adult weight change and risk of postmenopausal breast cancer. JAMA. 2006 Jul 12;296(2):193-201*
10. *Evans DG, Howell A. Breast cancer risk-assessment models. Breast Cancer Res. Review. 2007;9(5):213*
11. *Claus EB, Risch N, Thompson WD. Genetic analysis of breast cancer in the cancer and steroid hormone study. Am J Hum Genet. 1991 Feb;48(2):232-42.*
12. *Gail MH, Brinton LA, Byar DP et al. Projecting individualized probabilities of developing breast cancer for white females who are being examined annually. J Natl Cancer Inst. 1989 Dec 20;81(24):1879-86*
13. *Costantino JP, Gail, MH, Pee D, Anderson S, et al. Validation studies for models projecting the risk of invasive and total breast cancer incidence. J Natl Cancer Inst. 1999 Sep 15;91(18):1541-8*
14. *Cintolo-Gonzalez JA, Braun D, Blackford AL et al. Breast cancer risk models: a comprehensive overview of existing models, validation, and clinical applications. Breast Cancer Res Treat. 2017 Jul;164(2):263-284*

Annexing 1-(07.11.2021)-4.1.3.What is National Screening Mammography?

National Screening Mammography is a health service that enables female citizens of the Republic of Turkey between the ages of 40-69 to receive free breast cancer screening services. The medical rules of the relevant service are provided by the General Directorate of Public Health, and the information rules are provided by the General Directorate of Health Information Systems. The aforementioned service is provided through the National Screening Mammography System (MM Screening) in Cancer Early Diagnosis Screening and Training Centers, Healthy Life Centers and some state hospitals in Turkey's 81 provinces. Screening mammograms taken in these health institutions are reported via the National Screening Mammography Reporting System (MM Screening) with the teleradiology method.

4.1.3.1. How Are Reports Made in National Screening Mammography?

All mammography films taken within the scope of the National Screening Mammography are reported with the BI-RADS classification for double-blind scanning

through the National Screening Mammography System (MM Screening). The data and explanations in the reporting phase are given in Tables 2, 3, 4, 85 and Figure 13.

Table 2. BI-RADS Outcome Assessment Categories

BI-RADS Value	Description	Diagnostic Value
INSUFFICIENT	Report Due to Insufficient Graph Unwritten Image	Insufficient
BI-RADS 1-2	Negative or Benign Findings (Routine Scan)	Negative
BI-RADS 0	Additional Investigations Required (Refer to Hospital)	Positive
BI-RADS 4	Suspicious Findings (Transfer to Hospital)	Positive
BI-RADS 5	High Probability of Malignant Findings (Transfer to Hospital)	Positive

Table 3. Breast Morphologies in Mammography

Breast Structure Value	Description	Sensitivity to Mammography
A	Totally Fatty	Very High

B	Scattered Fibroglandular Densities	High
C	Heterogeneous Dense (Small Masses Can Be Hidden)	Medium
D	Extremely Dense (Decreased Mammographic Sensitivity)	Low

Table 4. Meanings of Suspicious Symptoms Reported on Mammography

Questionable Findings	Descripti on
Mass	Swelling, hardness or lump that feels different compared to other parts of the breast or the breast tissue in the same area of the other breast is called a breast mass.
Calcification	Calcification, which can be called calcification with another definition, is the accumulation of calcium in the breast tissue. These calcifications, which are too small to be felt, can be seen on a mammography.
Asymmetry	Densities in one breast and not observed in the opposite breast.
Structural Disorder	It can be observed as the pulling of the breast tissue without a mass in the middle of the breast tissue.

Figure.13. Breast Zones Aks: Armpit M: Central Section of Breast

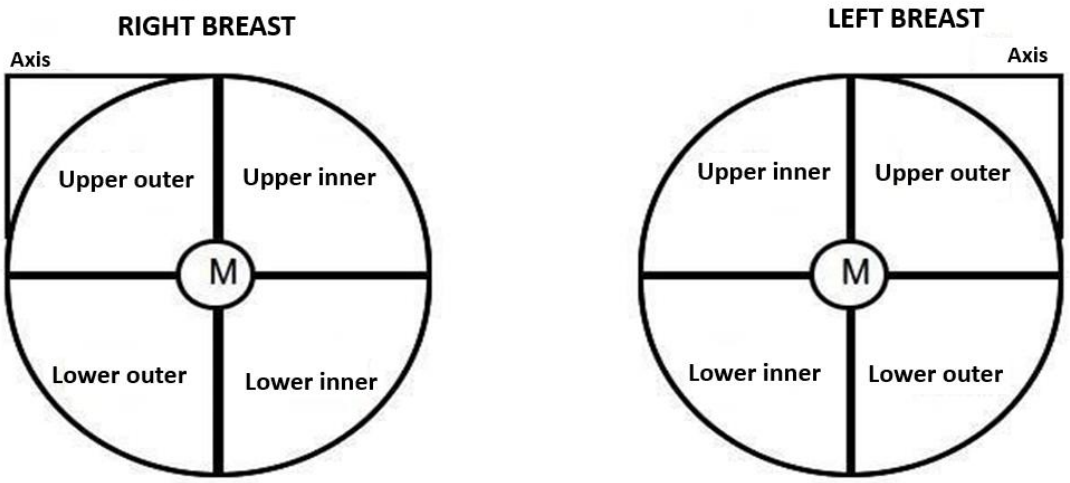


Table 5. Screening Mammography Reporting Unit

Reporting (Scoring) Eyes	**Description**
1st Eye	She/he is the first radiologist to score a mammography film in the system.
2nd Eye	It is the radiologist who scores the mammography film once scored without seeing the score result in the first eye in the system. There should be a different radiologist than the radiologist in the first eye.
3rd Eye	If the scores given by the radiologists in the first two eyes do not match according to the algorithm, it is the radiologist who scores a mammography film for the third time. There should be a different radiologist than the radiologist in the first two eyes.

4.1.3.2. How Does the Reporting Algorithm Function?

All mammography films taken within the scope of National Screening Mammography are concluded if the scores given by the 1st and 2nd eye radiologists are compatible. If there is inconsistency between the scores, the film in question is scored by the third eye radiology specialist.

The results and the compatibility status are determined by the following algorithms based on the data given in Table 2-3-4-5 and Figure 13.

The detailed algorithm of the National Screening Mammography Reporting is shown in Figure 15.

4.1.3.3. How Do Report Results Seem?

In the reports of all patients whose results are obtained in the National Screening Mammography Reporting System, patient information, the physician or physicians who wrote the report result, breast structure, suspicious findings, suspicious lesion location, BI-RADS result, advanced examination centers and some notes appear (Figure 14).

If there is compatibility between the opinions of 2 radiologists in the report of the patient with the result, the names of the 2 radiologists will also appear in the report. Only the name of one radiologist will appear on the report if there is no compatibility.

In all reports, at the bottom of the reports, there are advanced examination centers located in the province where the mammography was taken. In this way, the patient has information about the places to go for treatment (Figure 14).

Figure 14. Screening Mammography Report Example

Halk Sağlığı Genel Müdürlüğü
Kanser Daire Başkanlığı
Ulusal Tarama Mamografisi Raporlama Merkezi

KİŞİ BİLGİLERİ :

Erişim No	:	**TC Kimlik No**	:
Adı Soyadı	:	**Doğum Tarihi - Yaş**	:
İstem Tarihi	:	**İstemi Yapan**	:
Rapor Tarihi	:	**Raporlayan**	:

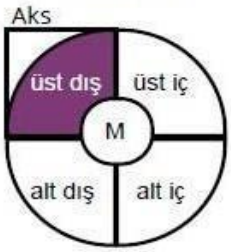
BILATERAL MLO VE CC TARAMA MAMOGRAFİSİ :

MEME YAPISI : **B** - Dağınık Fibroglandular Dansiteler

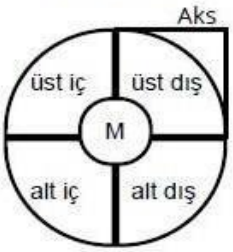
ŞÜPHELİ BULGULAR : **KİTLE**

ŞÜPHELİ LEZYON LOKASYONU :

SAĞ MEME



SOL MEME



SONUÇ :

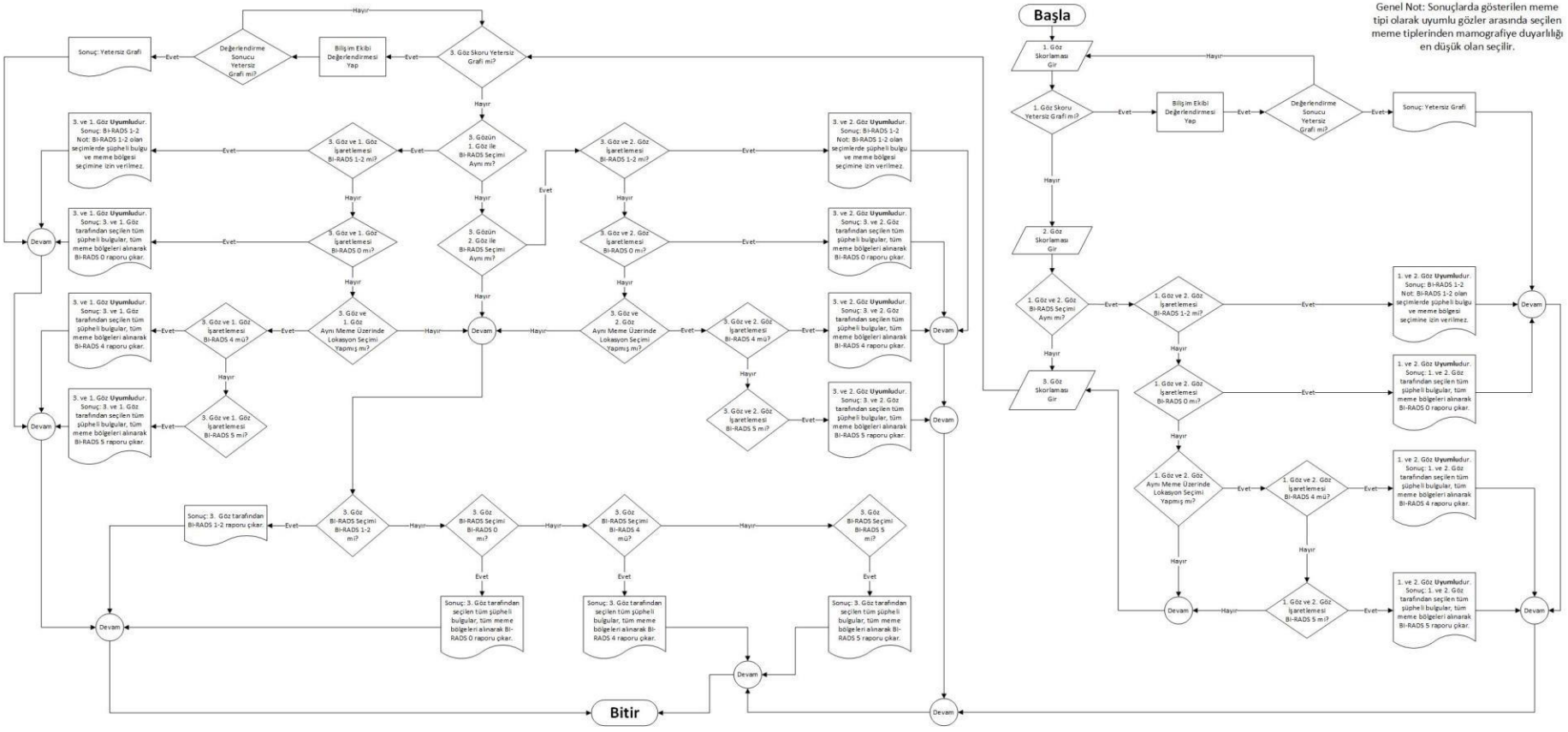
BI-RADS 4 - Şüpheli Bulgular (Hastaneye Sevk)

Önemli Bilgi!:

Ailede meme kanseri öyküsü varsa veya herhangi bir şikayetiniz olması durumunda (akıntı, ele gelen kitle gibi) sonucunuz negatif (BIRADS 1-2) olarak gelse bile mutlaka değerlendirilmek üzere uzman hekime başvurunuz!!!
Altın standart tarama yöntemi olarak kabul edilen mamografi taramasında yalancı negatiflik durumu genel olarak değerlendirildiğinde meme kanserlerinin %20'sinde görülmektedir. Bu nedenle;
Aylık Meme Muayenesi ve yılda bir klinik meme muayenenizi yaptırmayı ihmal etmeyiniz. 2 yılda bir rutin mamografi taramalarınıza devam ediniz.

Osmaniye İleri Tetkik Merkezleri : OSMANİYE DEVLET HASTANESİ, KADİRLİ DEVLET HASTANESİ

Figure 15. Detailed Algorithm of National Screening Mammography Reporting



4.1.4. Cancer Department Central Reading Report Result

Method

Advanced examinations of people who had screening in all provinces (2016-2018) were processed manually in the excel format. These forms, which were then forwarded to our Department, were combined.

Findings

According to the Excel database collected from the provinces, the final result of 965 (35.5%) of 2718 cases with BIRADS 5 is unknown. It was determined that 1633 (93.2%) of the remaining 1753 cases were cancer and 120 (6.8%) were
not cancer (Figure 4).

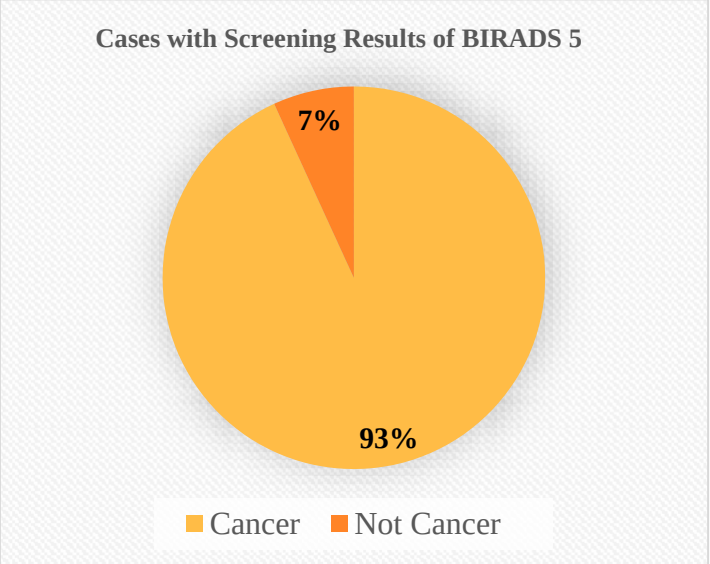


Figure 4 Distribution of Final Diagnoses of Cases with Screening Result of BI-RADS 5

According to the Excel database collected from the provinces, the final result of 3698 (65.6%) of 5632 cases with BIRADS 4 is unknown. It was determined that 1246 (64.4%) of the remaining 1934 cases were cancer and 688 (35.6%) were
not cancer (Figure 5).

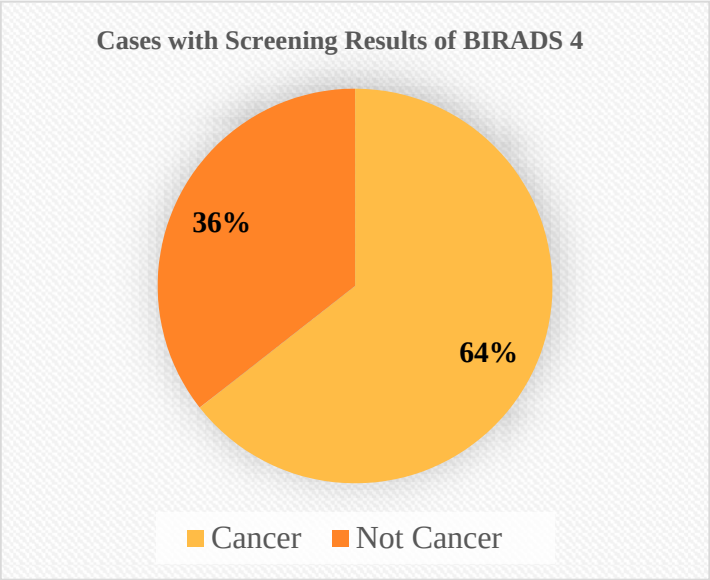


Figure 5 Distribution of Final Diagnoses of Cases with Screening Result of BI-RADS 4

According to the excel database collected from the provinces; The final result of 53139 (85.4%) of 62245 cases is not known and their screening result was BIRADS 0. It was determined that 848 (9.3%) of the remaining 9106 cases were cancer and 8258 (90.7%) were not cancer (Figure 6).

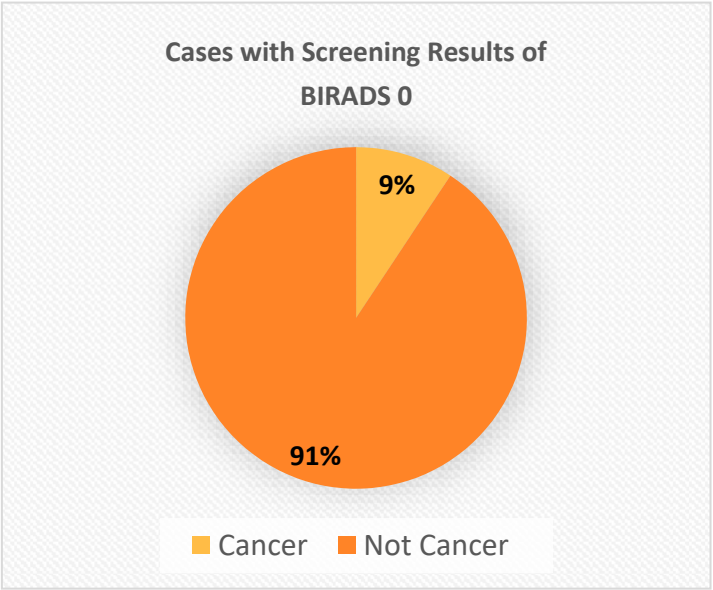


Figure 6 Cases with Screening Results of Brads 0

4.1.5. Cervical Cancer Screenings

When we look at the GLOBOCAN 2018 data, new global cancer data show that the global cancer burden has increased to 18.1 million cases per year and 9.6 million cancer deaths per year.

Cervical cancer is the fourth most common in women in the world, according to 2018 GLOBOCAN data. It is the only cancer in which we can see the precursor lesions and make an early diagnosis before the cancer starts in the patient. Cervical cancer screening programs have been successfully implemented in many countries around the world for years, and as a result, the morbidity and mortality rates of cervical cancer have been significantly reduced. Cervical cancer is no longer an important problem in developed countries, as developed countries implement screening programs properly. While it is seen in the 2nd place in developing countries, it has fallen to the 6th and even 10th place in some countries due to the successful implementation of screening programs in developed countries. However, cervical cancer is still seen as a very serious public health problem in underdeveloped or underdeveloped countries.

In 2018, approximately 570,000 women worldwide were diagnosed with cervical cancer, and approximately 311,000 women died from cervical cancer. Approximately 85-90% of these deaths are women living in underdeveloped countries. These numbers show how important screening programs in cervical cancer are in reducing the incidence of this cancer and the death rate from this cancer [1-2].

When we look at the world, we can see that the incidence is very high especially in Sub-Saharan Africa, South America, Eastern Europe and India (Figure 7).

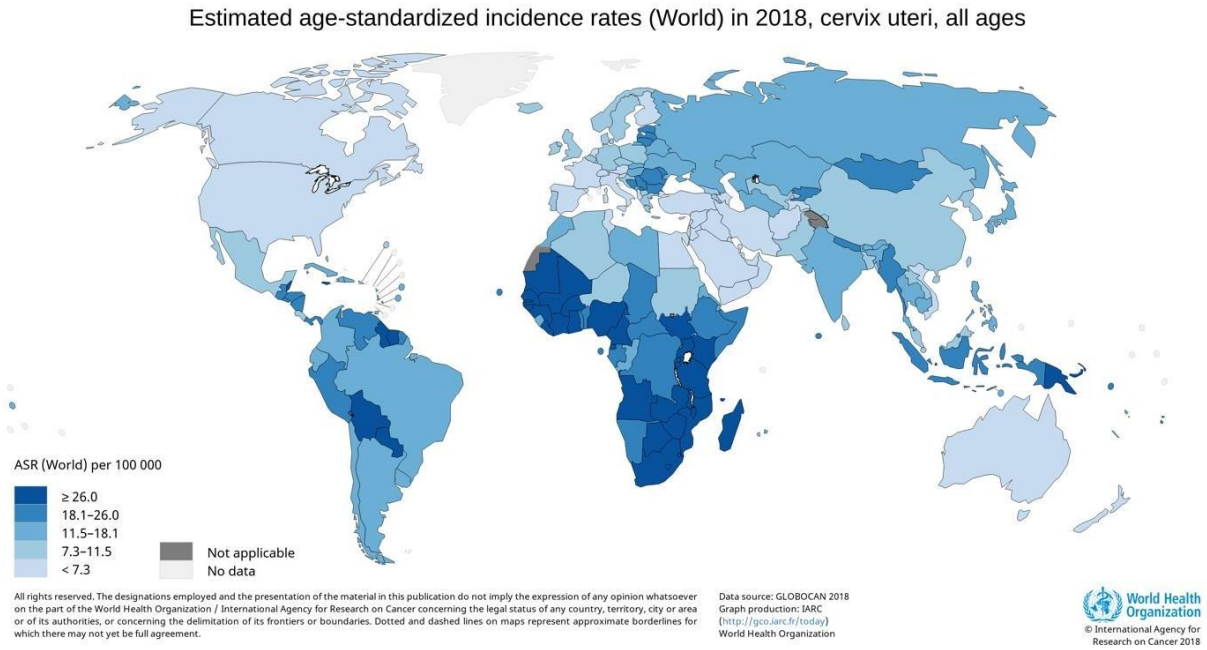


Figure 7. Cervical Cancer Incidence in the World (GLOBOCAN 2018)

Abnormal Cervical Cytology and Cervical Cancer in Turkey

According to the data of the Ministry of Health of the Republic of Turkey, 623 cervical cancers were detected in 1996 and while it was the 7th among all female cancers, this number increased to 708 in 2002, but fell to the 10th rank among all female cancers. While the number of cervical cancers increased to 763 in 2003 data, 9 it rose to the rank -- among all female cancers. According to the GLOBOCAN study conducted by the International Agency for Research on Cancer in 2002, the incidence of cervical cancer in Turkey is 4.5 per hundred thousand. It is expected that there will be 1364 new cases of cervical cancer and 726 deaths due to cervical cancer in the same year. According to GLOBOCAN 2008 data, the incidence is given as 4.2 per hundred thousand. According to the same data, 1443 new cervical cancer cases and 556 deaths due to cervical cancer are expected annually. Although there seems to be a decrease in the incidence according to 2008 GLOBOCAN data, these data do not fully reflect the figures for Turkey. In 2019, the last data of the Ministry of Health Cancer Department of the Republic of Turkey for 2016 were published. As a result of this study, while the incidence was 4.7 per hundred thousand in 2003, according to the figures of 2015, cervical cancer ranked 9th among female cancers and its incidence was found as 4.3 per hundred thousand (Figure 8).

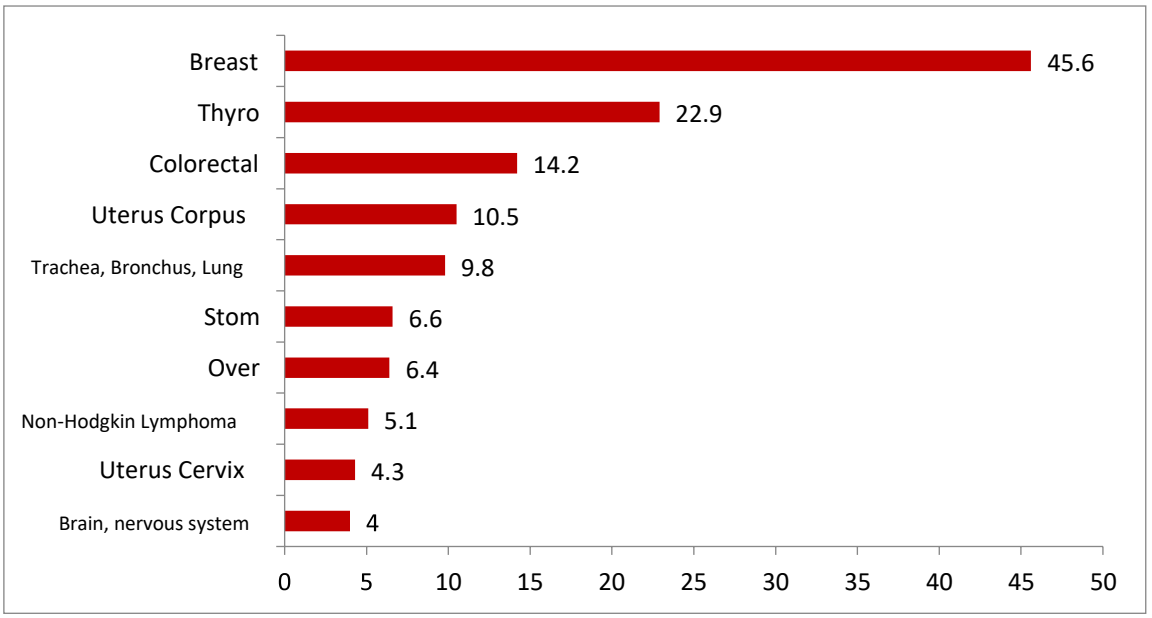


Figure 2 Age-Standardized Rates of 10 Cancer Types which are Most Common in females (Turkey Compositional database, 2016) (World Standard Population, per 100,000 individuals)

These figures show that the incidence of cervical cancer in Turkey is below that of many countries in the world that have developed and have national screening programs and carry out these programs very well. However, it shows a slightly increasing trend. Since the cervix is an easily accessible organ, early diagnosis can be made in cancers of this organ, thanks to Pap smear and HPV DNA Tests, and the prognosis improves significantly. The average age at diagnosis of patients with cervical cancer is 51. There are two peaks in this disease. The first is around 35-59 years old, and the second is around 60-64 years old. The lifetime risk of developing cervical cancer in a woman who has never had a Papanicolau (Pap) smear is 1/100.

In the USA, where statistics are the strongest, approximately 16,000 new cases of invasive cervical cancer are diagnosed annually and 5,000 deaths are expected from this disease, while the number of new cases expected in 2006 decreased to 9710 and death from the expected disease to 3700 due to the success of screening programs.[3]3 The biggest risk for cervical cancer is never having a Pap smear. In developed countries like USA, while 85% of women have had a Pap smear at least once in their lifetime, this rate is only 5% in underdeveloped countries.[4]4 Cytology and colposcopy and HPV DNA tests, which have increased in importance in recent years, are valuable tools in eliminating cervical cancer.

HPV DNA was found positive in 95% of squamous cell cancers and 90% of adenocarcinomas. As stated in preinvasive lesions, HPV 16 is mostly responsible for squamous cell carcinomas and HPV 18 is mostly responsible for adeno carcinomas, among the high-risk oncogenic HPV types [5]5

The first and most important population-based screening program in Turkey to date, "Reproductive Health Education in Şanlıurfa and Cervical Cancer Screening in Women", which was carried out in Şanlıurfa, is the result of the Reproductive Health Program in Turkey of the Ministry of Health of the Republic of Turkey, financed by the European Union. It is a program in which Ankara Middle East Lions Club participates as a non-governmental organization. At every stage of this program, T.R. Gynecology and obstetrics specialists of the Ministry of Health Ankara Etlik Zübeyde Hanım Gynecology Training and Research Hospital Gynecological Oncology Clinic also took part. The project was built and completed between January 2005 and January 2007 [6].6 The aim of the project was to raise public awareness about reproductive health and cervical cancer in Şanlıurfa, to initiate a promotional campaign, to screen for cervical cancer, to provide early diagnosis and treatment of cervical cancer, and to contribute to reducing deaths from this cancer. The duration of the project was 2 years and for this, 50,000 people in Şanlıurfa were trained for 2 years. Smears were taken from 10,000 women for early detection of cervical cancer. Two different cervical screening methods, VIA (Visuel Inspection of Acetic Acid) and VILI (Visuel Inspection of Lugol Iodine), which are used especially in developing countries for cervical screening, were applied to the patients at the same time. After the application of 3-5% acetic acid and lugol solution, direct visual inspection of the cervix was taught to the nurses in the region with a short-term training program. This training was carried out theoretically and practically in the company of experienced physicians. Abdominal and pelvic examinations were performed on the patients, speculum was inserted, and lesions that may be compatible with cervical cancer were first taught. Then, after applying diluted acetic acid and waiting for 1 minute, inspection of the cervix was performed under the light. Nurses were taught to make sure that the entire transformation zone was visible. According to the findings, the patients were evaluated as VIA negative or positive, VILI negative or positive. All patients who were screened in this way and the test was found to be positive, were performed colposcopy as an advanced examination and, if necessary, guided biopsy with colposcopy. 2500 of the women with suspicious lesions were reexamined, biopsies were

taken and their treatments were performed. The number of cervical cancers detected during the project remained below the rates seen in Europe. This suggests that cervical cancer is less common than expected in Turkey. With the project, it was a first in Turkey and one of the most important works in the world. In the project, a total of 380 midwives-nurses, 120 general practitioners, 250 teachers, 450 imams, 80 head people (muhktar), 70 volunteers working in various non-governmental organizations were trained. The screening of 10,000 women was completed in the project. Approximately 50,000 women were trained.

Cervical cancer screening:

Screening means administering a diagnostic test to an individual to look for an abnormality that they do not suspect or react to. The purpose of the examination in screening is to identify an early stage, pre-stage or risk factor of a disease.

Cancer screening is testing and examination to catch cancer in its early stages, when treatment can be much easier and more effective. Screening methods are applied in the period from the onset of the disease until the disease shows a visible symptom. Unfortunately, there is no effective screening method for every type of cancer.

Population-based screening is the periodic screening of cancers that can be screened with specified test or examination techniques in a specific target population.

The purpose of screening for cervical cancer is to reduce the incidence and mortality of invasive disease. If we look at the comprehensive and strong evidence from well-organized cytological screening programs, we see that this goal is achievable. In order to maximize the positive impact of screenings and minimize negative impacts, screening service should only be provided on regular basis. Designing a cervical cancer screening program includes defining the screening policy, i.e. determining the target age group, selecting the screening range for normal test results, choosing screening test systems, and determining follow-up and treatment strategies for women with positive screening results. The screening policy should take into account the variability of the increased risks of the target populations and take into account the natural history of the disease. A well-organized screening program should have a high level of public adoption, population coverage, and ensure and demonstrate high quality at all stages [9-12].

Community-based information systems should be established in order to continuously monitor the screening process indicators. An appropriate legal framework is required for recording personal data and linking population databases, screening files, and cancer and death registries. The informatics (data processing) system is one of the basic tools required for the management of the scanning program. It calculates indicators of participation, compliance, quality and impact, and provides feedback to involve health professionals, stakeholders and health authorities in the process. The design of a new screening program should be such that it allows for evaluation. An observation that a screening method detects more precursor lesions than a standard Pap smear is not sufficient to demonstrate increased effectiveness. More evidence is needed to determine whether the application of this new screening method will overly lead to unnecessary diagnosis and treatment (overdiagnosis and over-treatment) of a nonprogressive condition.

The screening policies, organization and practices in the countries of the world vary between countries. The same goes for effectiveness and cost-effectiveness. Ineffectiveness results from low screening coverage, uneven distribution, and sub-optimal screening program quality and screening standards. In order to maximize the positive impact and minimize the possible negative impacts, it is recommended that the screening service be provided under regular conditions [13-18].13-18).

Another issue is the scope and completeness of the information recorded. Reliable cancer registries are important. Links between individual data at the population level, screening level, cancer registry level, and treatment level are needed [13].

Evidence of the effectiveness and quality of each national program is required. Screening performance results should be regularly released to decision makers, staff, screeners, and participants, and the public that clearly demonstrate how well the program is being run. Other key elements of monitoring and evaluating the screening, are the scientific evaluation of the effectiveness and outcomes of the screening program based on established epidemiological methods, as well as clarification and feedback of information on invasive cancers detected during or following screening.

Cervical cancer screening requires the use of a test with high sensitivity and specificity for progressive intraepithelial lesions (CIN), which is easy to administer by healthcare personnel or allied health personnel, is available at a reasonable price, causes minimal discomfort to the woman, and has high sensitivity. Evidence of efficacy should be based on the potential to reduce cancer morbidity and mortality. High sensitivity is an insufficient criterion for detecting CIN because CIN often regresses. High specificity is required to avoid anxiety, unnecessary treatment and side effects.

Age Group to Target

One of the most discussed issues to date has been the age to start screening. Each country should set its own standards according to its own circumstances. No additional contribution was observed from starting screening at age 20 compared to starting screening at age 25. When planning to start a new program, resources should be focused on the age range from 30 or 35 to 60-65 years old. A good model would be to initiate screening 5 years before the age at which the age-based cervical cancer incidence curve peaks, according to the recommendations of the World Health Organization. High coverage rate should be the main target [19-21].

In a program that will start with HPV Tests, the beginning of the screening should be at least 30 years old. A screening program that will be started earlier with HPV tests will increase unnecessary interventions and patients' anxiety. Because many lesions that can heal spontaneously in this age group will be detected and treated unnecessarily.

There is no conclusive evidence as to what is the ideal age to stop screening. However, recent consensus is that screening should be terminated after the age of 65 if two negative test results are obtained [12,15].

Scan Range

According to the multicenter study of the International Center for Research on Cancer (IARC), 93% of the expected squamous cell carcinoma cases can be prevented if screened every year, 91% if screened every three years,
and 84% if screened every five years. A negative Pap smear result is associated with an extremely low risk of cervical cancer for at least 5 years [21].

However, it is considered unnecessary to perform screening with an interval of less than 5 years in screening with newly released HPV Tests [22-24].

Screening Approach: Population-based screening versus opportunistic screening

Previous reports on trends in cervical cancer incidence and mortality have shown a clear decline in countries or regions that have widely implemented population-based screening programs compared to countries that do not have screening programs or have only opportunistic screening. Therefore, regular population-based screenings appear to be a more effective and substantially more cost-effective method than opportunistic screenings. Community-based cervical cancer screening is a multi-stage process and should include the following stages:

- Determining the target audience
- Finding women eligible for screening
- Collection of Pap smears
- Examination and reporting of Pap smears
- Providing peace of mind to women with normal smear results and providing information about the timing of the next smear
- Re-calling women with unsatisfactory/insufficient smears
- Follow-up of women with abnormal smears, that is, application of diagnostic procedures and treatment if necessary. There should also be a failsafe system to ensure that this tracking is carried out.
- Recording, monitoring and evaluation of the entire program.

Scanning Methods

Conventional and Liquid Based Cytology:

Cells are collected from the surface of the uterine cervix and from the cervical canal with a spatula or brush, the cells are either spread directly on a glass slide or transferred to a liquid medium and then placed on the slide. Cells must be stained for microscopic evaluation by a cytologist. The cells are then analyzed using a microscope.

In liquid-based cytology (LBC), a cervical brush is often recommended to collect

the sample. However, it is also among the options to use a wide-tipped plastic spatula or endocervical brush together. The smear is not normally transferred onto a slide. The sample collection device carrying the material is immersed in a container containing a special liquid transport medium. This container is then sent to a specially equipped laboratory. Cytological screening every three to five years can reduce the morbidity and mortality of cervical cancer by 80% or more if conventional Pap smears are presented in regular and quality-assured conditions. The test validity of the conventional Pap smear for CIN, especially the cross-sectional test sensitivity, is moderate: in the range of 50 to 70% for CIN, but around 80% for high-grade CIN. There are reported false negative rates of 15-70% of cytological examinations. The incidence of false negative and inadequate Pap smears has led to the development of new technologies such as liquid-based cytology and automated screening devices.

Significantly higher test positivity rates were observed for LSIL and HSIL in studies with liquid-based cytology (LBC). In addition, the positive predictive value for histologically confirmed CIN 2+ (grade 2 or more serious disease) is not lower than for conventional cytology. These findings may suggest a higher sensitivity for LBC. However, the level of evidence to state this is low, due to poorly controlled and validated study designs. There was no statistically significant difference between the test sensitivities and specificities of conventional cytology and liquid-based cytology in terms of detecting CIN 2+ in studies.

In general, LBC has a lower sample rate and requires less time to interpret this test. The cost of a single LBC test is considerably higher, but allows for secondary molecular testing, such as the high-risk HPV test done in the case of ASC-US.

Cervical cytology has important limitations such as obtaining sufficient amount of cells from the right place, correct detection and labeling, and interlaboratory reproducibility rates. In addition, well-trained cytotechnicians and cytologists are needed in the countries where the program is implemented [12,15,19,21].

HPV Tests:

There is strong evidence to suggest that infection with the sexually transmitted human papillomavirus (HPV) is a necessary but insufficient etiological condition for cervical cancer formation. Moreover, only high-risk HPV types are associated with cervical cancer. Considering this evidence, several different applications have been proposed for the detection of HPV DNA: 1) primary screening for oncogenic HPV types alone or in combination with cytology, 2) triage of women whose cytology results are uncertain, 3) to predict the success or failure of the treatment, follow-up of women who have received CIN treatment [12, 21].

With clearly higher specificity and reproducibility for high-grade cervical epithelial lesions (HSIL), the human papillomavirus (HPV) DNA test has become widely accepted as the most important screening test in recent years. In recent studies, the sensitivity of many HPV tests has been found to be around 96%. The main concern for these tests is their lower level of specificity due to their temporary inability to distinguish from persistent infections. For this reason, HPV tests are only recommended for women over the age of 30 in screening programs.

Since the need for a sample representing the entire cervix for HPV testing is much less critical, screening with self-sampling of the patient provides a significant advantage for HPV testing. It provides the opportunity to broaden the scope of screening, particularly for women who avoid visiting a doctor or nurse for testing. There are early studies showing that this option is widely accepted by women [22,23].

Although the infrastructural requirements for effective screening for HPV are much less than for cytology, this is still one of the major obstacles in the poorer regions of the world that are most in need of screening. In these regions, the "see and treat" method for abnormal appearances, which we can accept as a form of assisted visual examination, requires minimal infrastructure and is the simplest. Although its performance is not as good as the HPV test, it is still important to be recommended in such cases [22].

Approximately seventy percent of invasive cervical cancers worldwide are associated with HPV16 and 18 infection. In 2005, Khan et al. reported that of the approximately 20,500 women who participated in routine cervical cancer screening, those with HPV16 or HPV18 had a significantly higher 10-year cumulative CIN3 and cancer risk than those who were positive for non-16/18 high-risk HPV (hrHPV) (17%, 14%, and 3%, respectively). Many subsequent studies have confirmed that HPV16 or HPV18 positive women are at higher risk for absolute CIN3+ (24,25).

These observations have significantly increased the role of HPV16/18 genotyping in cancer screening, particularly in prioritizing emergency colposcopy in HPV16/18-positive women over 30 years of age, as well as the commercial validity of HPV diagnostic tests that yield HPV16/18-specific results.

One of the most important recent studies on more than 40,000 women is the ATHENA study [18,19]. Similar to strategies applied only to women with ASC-US or more severe cytology in this study, strategies applied only to HPV16- or 18 positive women sensitive to detection of CIN3+, suggests that prioritization of hrHPV positive screening tests by cytology or HPV 16/18 genotyping is equally applicable. Analyzes of another population-based screening study in the Netherlands evaluated similar prioritization pursuits and revealed that prioritizing hrHPV-positive women by cytology, based on a proportional balance of benefit (high negative predictive value) and harms (reasonable referral rate to colposcopy), is the preferred strategy [28].

The value of performing specific genotyping for types other than HPV16 and 18 is uncertain. Contrary to Kaiser's study [24], studies conducted in Denmark[25], the Netherlands[(29)] and Sweden[(30)] indicated an absolute risk for women with HPV31 and HPV33 to progress to HSIL similar to women with HPV16/18. Matsumoto et al. [(31)] found a 20.5% risk of progression of low-risk (LSIL) lesions to high-risk lesions (HSIL) in women with HPV16, 18, 31, 33, 35, 52, and 58, whereas he reported this rate as 6.0% for other hrHPV types. It remains to be determined whether there are actual type-specific geographic differences in disease risk, or whether differences in study plan and HPV or disease investigation protocol or a simple possibility explain the observed non-compliance.

Prioritization strategies with genotyping primarily target those aged 30-35 years and

above. However, the rate of HPV16/18 positive CIN3+ in older women is significantly lower than in younger women. For example, in the ATHENA study, only 35.8% of CIN3 lesions in women over the age of 40 were HPV16 or 18 positive, compared with 60% in women aged 30-39. Considering the age-related differences in type characteristics in older women, it is necessary to take into account that type-specific prioritization strategies may require stratification for those aged around 30 years and above.

HPV genotyping offers a reasonable strategy to reduce over-referral to colposcopy in prioritizing hrHPV-positive women. Modeling studies have suggested that this approach is more cost-effective. However, prospective studies comparing HPV genotyping and cytological prioritization performances in hrHPV positive women are needed. The article published by Meijer CJ in 2009 still sets a standard for HPV testing [24].

The study by Ronco et al., on the other hand, showed that the sensitivity of using HPV test in screening is quite high, and the rate of high-grade cervical lesions and cervical cancer missed in screenings is much less [25,26].

The ineffectiveness of adding cytology to HPV tests was also demonstrated in the meta-analysis of Arbyn et al. published in 2012 [(35, 36)].

p16 INK4a:

It is a marker for the transforming activity of the cyclin-dependent kinase inhibitor p16INK4a, hrHPV oncoproteins required for the initiation and maintenance of the neoplastic process. There are several clinical research studies in the evaluation of cervical histology and cytology specimens that show a strong link between immunochemical staining with p16INK4a and overexpression of p16INK4a and cervical neoplasia [37,38].

In histology, a strong staining of basal and parabasal squamous cell portions with p16INK4a is present and is considered positive staining. Staining with p16INK4a greatly assists pathologists in making the histopathological diagnosis of cervical lesions. The use of p16INK4a immunohistochemistry is an essential tool in improving diagnostic accuracy, reliability, and quality in the histopathology of cervical lesions.

ProExC Test:

In a direct comparison study with p16INK4a, the ProExC marker panel showed

higher sensitivity in detecting women with LSIL but lower specificity in identifying high-grade squamous intraepithelial lesion cases (HSIL). Triage with ProExC after primary HPV screening significantly increased sensitivity (ratio: 1.30) and PPV (ratio: 2.89). It was the best performer of the eight strategies examined by modelling, achieving a further 55% reduction in the proportion of patients referred for colposcopy [0–42].

E4 and L1:

HPV-infections require independent differentiation of squamous epithelial keratinocytes. Viral proteins involved in the late phase of the replication cycle, such as the L1 capsid protein or the E4 protein, are only expressed in HPV-infected squamous epithelial cells that are capable of fatally differentiating and replicating HPV-particles. Therefore, detection of late gene products E4 or L1 has been suggested as markers for CIN1 in histology or LSIL in cytology samples. E4 is complementary to E6/E7 proxies (such as MCM, Ki67 or p16INK4a) as a result of accumulation of E4 protein in infected cell by cell proliferation arrest via E6/E7. The presence of the viral protein marker appears to be helpful in distinguishing between viral and non-viral CIN1 and lesions falling into the suspected CIN2 category. Further studies are needed to fully evaluate the utility of E4 as a complementary marker in disease staging in histology [43].

Methylation of host cell genes:

In recent years, many studies have pointed to genetic changes in HPV-infected host cells (epi) that work as molecular disease markers of malignant cervical disease. Among these, the DNAme of various host genes attracts the majority of attention. The fact that atypical methylation is readily detectable in cervical smears up to 7 years before cervical cancer diagnosis supports the idea that host gene methylation analysis is a valuable, alternative prioritization tool in hrHPV DNA-positive women. In addition, methylation of certain genes is much more specific for cervical adenocarcinoma (*in situ*). Methylation analyzes can be applied not only to swab samples but also to self-collected cervico-vaginal lavage samples, providing the possibility of all primary and reflex prioritization testing algorithms [44–46].

Methylation of viral genes:

The functional significance of viral DNAme, including patterns in the HPV genome,

and the relationship of this phenomenon to CIN and cancer have been discovered with increasing interest over the past years. While a great deal of information is available about DNAme within HPV16 and up to a point HPV18, information on other HPV genomes is much less. In particular, while only a very small percentage of individuals with hrHPV-infection eventually develop cancer, the search continues for sensitive predictive testing to prioritize women who are often referred for colposcopy. DNAme analyzes can satisfy this need for prioritization [46].

Turkey Cervical Cancer Screening Program:

Cervical Cancer has been screened with cervical smear and opportunistic screening since 1992 in Turkey. Adapting the WHO recommendations to the conditions of our country, the Cancer Department has planned for asymptomatic women in the 30-65 age group to have a cervical smear every 5 years at the Cancer Early Diagnosis Screening and Training Centers established across the country. This smear-based screening, which has been performed for a long time in our country, could not reach the targeted coverage rate of 70% due to many reasons. 20% of the female population planned to be screened could be screened within the scope of the screening program. In order to overcome the problems in cervical cancer screening, it was decided to change the screening strategy. For this purpose, opinions were sought from domestic and foreign experts, institutions and organizations. In the light of current opinions, it was decided in December 2012 that cervical screening should be performed primarily with HPV tests, with the scientific commission meeting. With the opinions taken from various foreign and domestic specialty associations and experts, it was decided that primary HPV testing would be a good and cost-effective solution for cervical screening in our country, considering the quality and increasing coverage. According to the renewed national cancer screening standards, every woman in the 30-65 age group is planned to be screened with HPV test every 5 years, and the positive cases to be re-evaluated with a smear, and a new program was started in 2014. In 2020, the algorithm of the program was renewed and it is given in **Figure 9**.

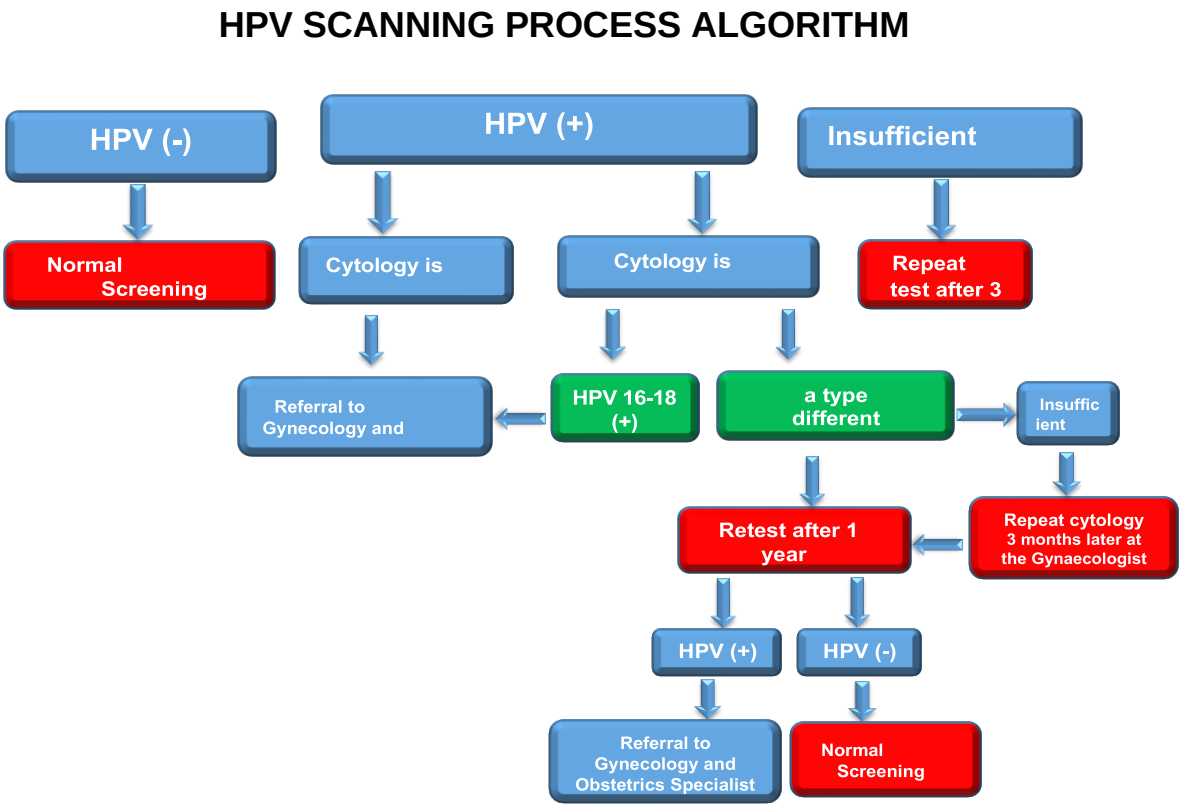


Figure 9 Turkey Cervical Screening Program New Algorithm.2020

The data obtained from 4 million women of the Turkey Cervical Cancer Screening Program, which has been ongoing since 2014, was published in the July 2020 issue of the Gynecologic Oncology journal.

When we look at the summary of the study, a total of 4,099,230 women participated in cervical cancer screening with HPV-DNA testing during this period. It was found that 4.39% of them were HPV-DNA positive. The most common HPV type was 16, followed by 51, 31, 52, 56 and 18 across all age ranges and geographic regions. Cytology results were reported as normal 69.2%, undersampling 16.6%, and abnormal ≥ASC-US in the remainder. Current screening with HPV DNA found 24.3% PPV for ≥CIN2. Comparing PPV for CIN2 + according to different HPV genotypes, it was found to be 32.6% for HPV 16, 15.3% for HPV 18, and for HPV 33, 31, 45 and 35,
34.4%, 19.3%, 15.3% and 14.0%, respectively.

This study includes the world's largest series summarizing real-world experience in a single

visit with primary HPV DNA screening and triage. The results demonstrate the feasibility of this screening method in developing countries with acceptable colposcopy referral rates. Among the triage tests, only pap-smear seems to be effective without the need for extended genotyping.

World Health Organization Cervical Cancer Elimination Program

Deciding that cervical cancer is an important public health problem in the world, WHO launched the Cervical Cancer Elimination Program in 2020. According to this program, the organization, which decided that a global struggle is needed, not one by one, recommended screening programs and HPV vaccination to all countries. If this program is realized, by 2030, 90% of girls who have reached the age of 15 all over the world have had HPV vaccine, 70% of women aged 35-45 have been screened with a highly sensitive test and 90% of women diagnosed with cervical disease can access treatment and care. (Fig.10). According to this program, the incidence of cervical cancer will have decreased to less than 4/100,000 worldwide in 2090 and will be eliminated in 2120 (Figure 11).

Figure 10. WHO Cervical Cancer Elimination Programme 2030 Targets

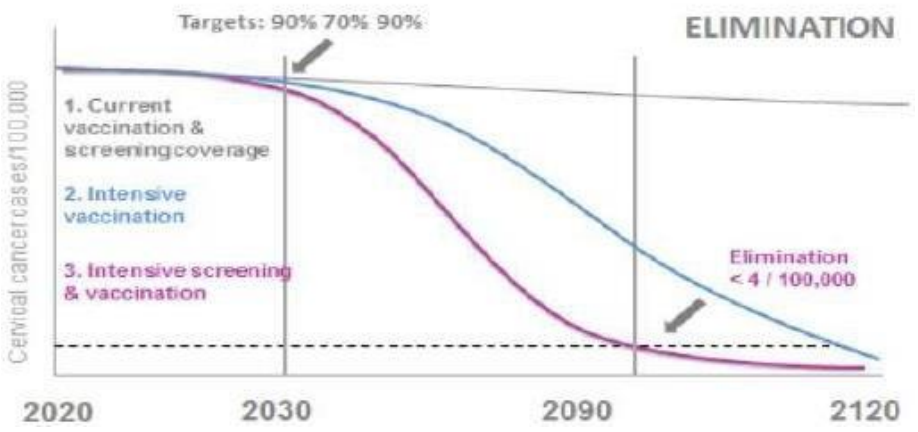


Figure 11 WHO Cervical Cancer Elimination Programme 2030, 2090, 2120 Targets

RESOURCES

1. Parkin DM, et al. Int J Cancer 1999; 80:827–41. (Worldwide CA incidence, 1990)
2. Pisani P, et al. Int J Cancer 1999; 83:18–29. (Worldwide CA mortality, 1990)
3. Greenlee RT. Hill-Harmon MB. Murray T. Thun M. Cancer Statistics, 2001. CA Cancer J Clin. 2001 Jan-Feb; 51 (1): 15-36. Erratum in: CA Cancer J Clin 2001;51:144.
4. Kuo DY, Goldberg GL. Screening of cervical cancer: where do we go from here? Cancer Ivest. 2003; 21(1):157-61.
5. Wright T.C. Jr, Schiffman M. adding a test for human papillomavirus DNA to cervical cancer screening. N Engl J Med. 2003, 6;348:489-90.
6. Tuncer M, Cancer Control in Turkey 2008, The Ministry of Health of the Republic of Turkey, Department of Cancer Control, Ministry Publication Number: 740, Ankara, Ministry of Health of Turkey.
7. Umudum H. I. Ulusal Sitopatoloji Kongresi Abstract Kitabı.
8. Prevalence of cervical cytological abnormalities in Turkey. Turkish Cervical Cancer And Cervical Cytology Research Group. Int J Gynaecol Obstet. 2009; 106:206-9.
9. Advisory Committee on Cancer Prevention & Lynge E. Recommendations on cancer screening in the European Union. Advisory Committee on Cancer Prevention. Eur J Cancer 2000; 36: 1473-1478.
10. Anttila A., Ronco G., Clifford G., Bray F., Hakama M., Arbyn M., & Weiderpass E. Cervical cancer screening programmes and policies in 18 European countries. Br. J. Cancer 2004; 91: 935-941.
11. Arbyn M., Autier P., & Ferlay J. Burden of cervical cancer in the 27 member states of the European Union: estimates for 2004. Ann.Oncol 2007; 18: 1425-1427.

12. Arbyn M, Anttila A, Jordan J, Ronco G, Schenck U, Segnan N, Wiener H, Herbert A, von Kars'a L. Ann Oncol. European Guidelines for Quality Assurance in Cervical Cancer Screening. Second edition--summary document. 2010 Mar;21(3):448-58.
13. Bray F., Sankila R., Ferlay J., & Parkin D.M. Estimates of cancer incidence and mortality in Europe in 1995. Eur J Cancer. 2002; 38: 99-166.
14. Davies P., Arbyn M., Dillner J., Kitchener H., Ronco G., & Hakama M. A report on the current status of European research on the use of human papillomavirus testing for primary cervical cancer screening. Int. J. Cancer 2006; 118: 791-796.
15. European Commission (2003). Proposal for a Council Recommendation on Cancer Screening (presented by the Commission). Brussels, 5.5.2003. C0M(2003) 230 final. 2003/0093 (CNS), 1-21.
16. IARC Cervix Cancer Screening. IARC Handbooks of Cancer Prevention 2005; Vol. 10. IARCPress, Lyon
17. Insinga R.P., Glass A.G., & Brenda B.R. Diagnoses and outcomes in cervical cancer screening: a population-based study. Am. J. Obstet. Gynecol 2004;191: 105-113.
18. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics 2002. CA Cancer J. Clin 2005; 55:74-108.
19. Parkin DM, Whelan SL, Ferlay J, Teppo L, Thomas DB, eds. Cancer Incidence in Five Continents 2002; IARC Sci. Publ. No. 155, Vol. VIII. Lyon. IARC Press
20. Sasieni P., Adams J., & Cuzick J. Benefit of cervical screening at different ages: evidence from the UK audit of screening histories. Br. J. Cancer 2003; 89: 88-93.
21. WHO (2002). National Cancer Control Programmes. Policies and Managerial Guidelines, 2nd edition. World Health Organization, Geneva.
22. Cuzick J, Bergeron C, von Knebel Doeberitz M, Gravitt P, Jeronimo J, Lorincz AT, J L M Meijer C, Sankaranarayanan R, J F Snijders P, Szarewski A. New technologies and procedures for cervical cancer screening, Vaccine. 2012 Nov 20;30 Suppl 5:F107-16.
23. Castle PE, de Sanjosé S, Qiao YL, Belinson JL, Lazcano-Ponce E, Kinney W. Introduction of human papillomavirus DNA screening in the world: 15 years of experience.Vaccine. 2012 Nov 20;30 Suppl 5:F117-22.
24. Khan MJ, Castle PE, Lorincz AT, Wacholder S, Sherman M, Scott DR, et al. The elevated 10-year risk of cervical precancer and cancer in women with human papillomavirus (HPV) type 16 or 18 and the possible utility of type-specific HPV testing in clinical practice. J Natl Cancer Inst 2005;97(14):1072–9.
25. Kjaer SK, Frederiksen K, Munk C, Iftner T. Long-term absolute risk of cervical intraepithelial neoplasia grade 3 or worse following human papillomavirus infection: role

of persistence. J Natl Cancer Inst 2010; 102:1478–88.

26. Castle PE, Stoler MH, Wright Jr TC, Sharma A, Wright TL, Behrens CM. Performance of carcinogenic human papillomavirus (HPV) testing and HPV16 or HPV18 genotyping for cervical cancer screening of women aged 25 years and older: a subanalysis of the ATHENA study. Lancet Oncol 2011;12: 880–90.
27. Wright Jr TC, Stoler MH, Behrens CM, Apple R, Derion T, Wright TL. The ATHENA human papillomavirus study: design, methods, and baseline results. Am J Obstet Gynecol 2012;206(1):46e1–11.
28. Rijkaart DC, Berkhof J, van Kemenade FJ, Coupe VMH, Hesselink AT, Rozendaal L, et al. Evaluation of 14 triage strategies for HPV DNA-positive women in population-based cervical screening. Int J Cancer 2012;130(3):602–10.
29. Berkhof J, Bulkmans NWJ, Bleeker MCG, Bulk S, Snijders PJF, Voorhorst FJ, et al. Human papillomavirus type-specific 18-month risk of high-grade cervical intraepithelial neoplasia in women with a normal or borderline/mildly dyskaryotic smear. Cancer Epidemiol Biomarkers Prev 2006;15(7):1268–73.
30. Naucler P, Ryd W, Tornberg S, Strand A, Wadell G, Hansson BG, et al. HPV typespecific risks of high-grade CIN during 4 years of follow-up: a population-based prospective study. Br J Cancer 2007;97(1):129–32.
31. Matsumoto K, Hirai Y, Furuta R, Takatsuka N, Oki A, Yasugi T, et al. Subsequent risks for cervical precancer and cancer in women with low-grade squamous intraepithelial lesions unconfirmed by colposcopy-directed biopsy: results from a multicenter, prospective, cohort study. Int J Clin Oncol 2012;17(3):233–9.
32. Meijer CJ, Berkhof H, Heideman DA, Hesselink AT, Snijders PJ. Validation of high-risk HPV tests for primary cervical screening. J Clin Virol. 2009 Nov;46 Suppl 3: S1-4.
33. Ronco G, Segnan N. HPV testing for primary cervical cancer screening. Lancet. 2007 Nov 24;370(9601):1740-2. Epub 2007 Oct 4.
34. Ronco G, Giorgi-Rossi P, Carozzi F, Confortini M, Dalla Palma P, Del Mistro A, Ghiringhello B, Girlando S, Gillio-Tos A, De Marco L, Naldoni C, Pierotti P, Rizzolo R, Schincaglia P, Zorzi M, Zappa M, Segnan N, Cuzick J; New Technologies for Cervical Cancer screening (NTCC) Working Group. Efficacy of human papillomavirus testing for the detection of invasive cervical cancers and cervical intraepithelial neoplasia: a randomised controlled trial. Lancet Oncol. 2010 Mar;11(3):249-57. doi: 10.1016/S1470-2045(09)70360-2.
35. Arbyn M, Ronco G, Anttila A, Meijer CJ, Poljak M, Ogilvie G, Koliopoulos G, Naucler P, Sankaranarayanan R, Peto J. Evidence regarding human papillomavirus testing in secondary prevention of cervical cancer. Vaccine. 2012 Nov 20;30 Suppl 5: F88-99.

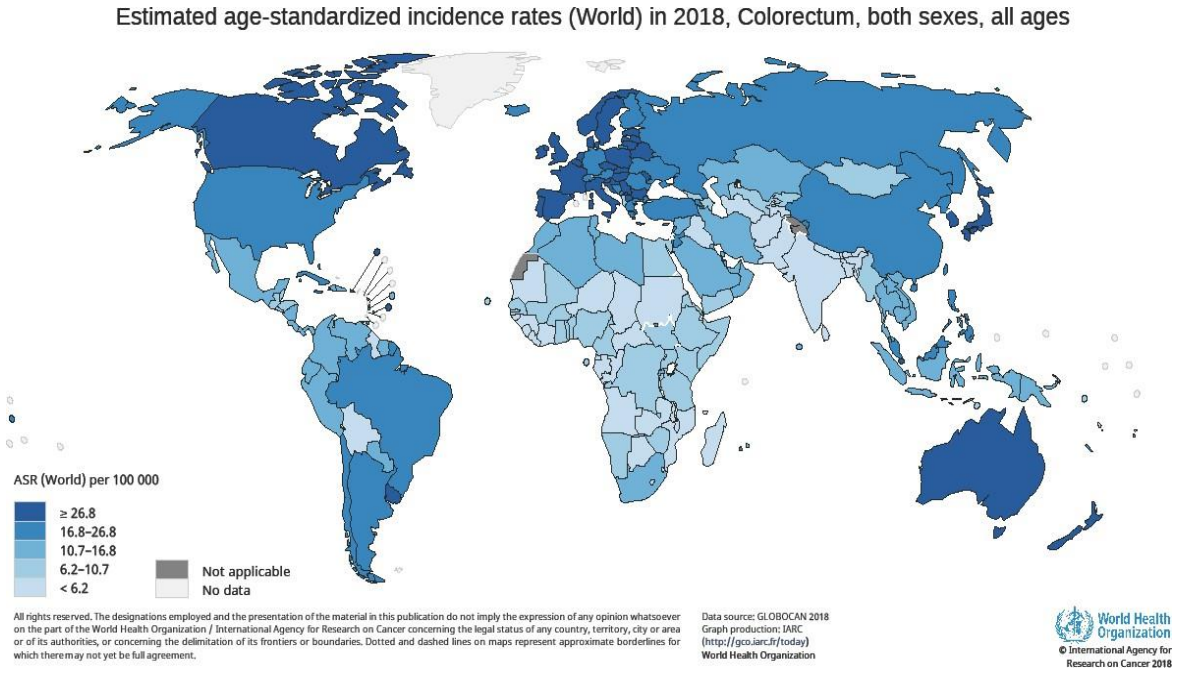
36. Dillner J. Primary human papillomavirus testing in organized cervical screening.
37. Curr Opin Obstet Gynecol. 2013 Feb;25(1):11-6.
38. Klaes R, Friedrich T, Spitkovsky D, Ridder R, Rudy W, Petry U, et al. Overexpression of p16INK4a as a specific marker for dysplastic and neoplastic epithelial cells of the cervix uteri. Int J Cancer 2001; 92:276–84.
39. Bergeron C, Ordi J, Schmidt D, Trunk MJ, Keller T, Ridder R. Conjunctive p16INK4a testing significantly increases accuracy in diagnosing high-grade cervical intraepithelial neoplasia. Am J Clin Pathol 2010; 133:395–406.
40. Boucher J, Anku-Bertholet C, Temmar R, Pelmus M. Evaluation of p16INK4a, minichromosome maintenance protein 2, DNA topoisomerase IIalpha, ProEx C, and p16INK4a/ProEx C in cervical squamous intraepithelial lesions. Hum Pathol 2009; 40:904–5.
41. Walts AE, Bose S. p16, Ki-67, and BD ProExC immunostaining: a practical approach for diagnosis of cervical intraepithelial neoplasia. Hum Pathol 2009; 40:957–64.
42. Depuydt CE, Makar AP, Ruymbeke MJ, Benoy IH, Vereecken AJ, Bogers JJ. BDProExC as adjunct molecular marker for improved detection of CIN2+ after HPV primary screening. Cancer Epidemiol Biomarkers Prev 2011; 20:628–37.
43. Robertson KD. DNA methylation and human disease. Nat Rev Genet 2005; 6:597–610.
44. Lorincz AT. The promise and the problems of epigenetics biomarkers in cancer. Expert Opin Med Diagn 2011; 5:375–9.
45. Bocklandt S, Lin W, Sehl ME, Sanchez FJ, Sinsheimer JS, Horvath S, et al. Epigenetic predictor of age. PLoS One 2011; 6:1–6.
46. Wentzensen N, Sherman ME, Schiffman M, Wang SS. Utility of methylation markers in cervical cancer early detection: appraisal of the state-of-the-science. Gynecol Oncol 2009 Feb;112(2):293–9
47. Kalantari M, Calleja-Macias IE, Tewari D, Hagmar B, Lie K, Barrera-Saldana HA, et al. Conserved methylation patterns of human papillomavirus type16 DNA in asymptomatic infection and cervical neoplasia. J Virol 2004;78: 12762–72
48. https://hsgm.saglik.gov.tr/tr/kanser-taramalari
49. Murat Gultekin, Selin Dundar, Bekir Keskinkilic, Murat Turkyilmaz, Nejat Ozgul, Kunter Yuce, Fatih Kara, Gynecol Oncol.2020 Jul;158(1):105-111.
50. https://www.who.int/docs/default-source/cervical-cancer/cervical-cancer-elimination-strategy-updated-11-may-2020.pdf?sfvrsn=b8690d1a_4

4.1.6. Colorectal Cancer

Current Situation in the World

While approximately one and a half million colorectal cancer (CRC) diagnoses are made worldwide each year, 750,000 patients die due to CRC [1]. According to the cancer registry center data of the Ministry of Health in fourteen provinces in 2016, it ranks third among all cancers with 14.2% in women and third in men with 25.3% in terms of incidence of CRC [2]. Colon tumors grow slowly and by the time they become symptomatic, the disease is usually advanced [3,4]. The diagnosis of CRC is made at an early stage (localized disease stage) in only 40% of patients. The prognosis in CRC is closely related to the stage at the time of diagnosis. Cancer should be able to be diagnosed in asymptomatic patients, for this it is necessary to inform the society and implement screening programs. The probability of detecting precancerous lesion or early stage tumor is high as a result of screening. Studies have shown that screening and follow-up reduce CRC mortality [3,4,5]. For a successful screening program, it is very important for physicians to be aware of this issue, to determine the risk, to make recommendations in accordance with the guidelines, to make an early diagnosis, to direct the treatment as soon as possible and to follow the patient [5].

Figure 12. Colorectal Cancer Incidence in the World (Globocan 2018)



Epidemiology and Incidence

The incidence and mortality of CRC varies markedly worldwide [5]. Worldwide, approximately one and a half million CRC diagnoses are made each year, while 750,000 patients die due to CRC [1]. The highest incidences are in North America, Australia, Northern and Western Europe, while low rates are found in developing countries, especially in Asia and Africa [5]. This geographical variation appears to be due to diet, environmental exposure, and genetic predisposition [7]. Age is the greatest risk factor for sporadic CRC. While CRC is rare under the age of 40, the incidence starts to increase after the age of 40-50 [5]. While 90% of CRC
cases are over the age of 50, this rate increases to 10% for men and 15% for women over the age of 80. The lifetime prevalence of CRC is around 2.4-5%. This rate increases with certain risk factors present in the individual [8].

Colorectal Cancer Risk Factors

Environmental and genetic factors increase the likelihood of developing CRC [9]. Although the greatest increased risk is genetically based, the majority of CRCs are sporadic rather than familial cancer [10]. Although Familial Adenomatosis Polyposis Coli (FAP) and Hereditary Non-polyposis Colorectal Cancer (HNPCC) are the most common familial colon cancers, they account for less than 5% of CRC cases [11].

Risk Factors That May Affect Screening Recommendations

A family history of colon cancer, a family or individual diagnosis of adenoma or CRC, or an individual with inflammatory bowel disease may change screening recommendations [12].

Family or Personal History of Adenoma/CRC

Those with a history of CRC or adenomatous polyps have an increased risk of developing CRC in the future. In patients undergoing single-focal CRC resection, the rate of metachronous primary cancer development at five years after the operation is between 1.5 and 3 [13]. A history of villous/tubulovillous polyps (especially if multiple) and adenomatous polyps larger than 1 cm increase the risk of CRC. It is known that many isolated tubular adenomas below 1 cm do not increase the risk [14]. Family history is also an important risk factor, apart from genetically predisposed syndromes. If there is a history of

CRC in one first-degree relative, the percentage of developing CRC is 1.7 times higher than in the general population. This rate increases more if there are two first-degree relatives with a history or the age of diagnosis is below 55 years [15]. If there is a family history of adenoma larger than 1 cm or villous/tubulovillous adenoma, there is an increased risk, as if there was a family history of CRC [13].

Inflammatory Bowel Disease

There is a close relationship between ulcerative colitis and colonic neoplasia. This relationship is directly proportional to the severity and duration of the disease. Pancolitis increases the risk 5-15 times compared to the general population. Left-sided disease was associated with a threefold relative risk, whereas those with proctitis alone did not have a significant increased risk [16]. For people with a 10-20 year history of inflammatory bowel disease, the incidence of CRC is around 0.5% per year. For the following years, this rate is 1%. According to most sources, coexistence of ulcerative colitis and primary sclerosing cholangitis increases this risk (17). Some sources also consider pseudopolyps, especially large and complex ones, to be an independent risk factor for CRC (18). There is also a relationship between disease activity and the risk of dysplasia and cancer (19). Although few sources are available, there is also a relative risk-increased relationship between pancolitis due to Crohn's disease and colon malignancy (20). Systemic inflammation in these diseases may also be a risk factor for CRC. In a controlled study, it was found that increased C-reactive protein level in low-risk patients was associated with an increased risk of CRC (21). However, this relationship was not found by some researchers (22).

Risk Factors That Do Not Change Screening Recommendations:

There are many factors that have little or no clear relationship with CRC, from environmental factors and lifestyle changes. There are many factors that have little or no clear relationship with CRC, from environmental factors and lifestyle changes. Most evidence suggests that DM is associated with an increased risk in CRC [23]. In a meta-analysis of 15 studies (six case-control, nine cohorts) with a total of 2,593,935 cases, the risk of CRC was found to be around 30% higher in diabetics than in nondiabetics [24]. The relationship between cholecystectomy and right colon cancers has been shown in some studies. A slight increase in right colon tumors was observed in 278,460 patients followed for 33 years after cholecystectomy (1.16 fold). Many meta-analyses establish this association

among right colon tumors [25]. The relationship between alcohol use and increased risk of CRC has been demonstrated in many studies [26]. Two large prospective cohort studies demonstrated that obesity increases the risk of developing CRC 1.5-fold [27,28]. Obesity also increases the mortality rate of CRC [29]. Coronary artery disease is also a risk factor for CRC [30]. Although the underlying cause of this relationship is not clearly seen, the fact that the diseases share common risk factors may be the reason for the increased risk [12]. Cigarette smoking has been associated with both an increased risk for CRC and death from CRC. Smoking is also a risk factor for the development of adenomatous polyps and high-risk polyps (large and dysplastic) [31]. In ureterocolic anastomoses after extensive bladder operations, the risk of developing neoplasia in the region close to the ureteral opening is increased [32]. Numerous sources indicate that long-term consumption of red meat or processed meat is associated with an increased risk of CRC, particularly left colon tumor [33]. The link between caffeine consumption and CRC risk is not clear. The link between non-familial BRCA gene mutations and colon cancer is unclear. It is known that the risk of colon cancer increases approximately twice in BRCA1 mutation carriers [34]. Radiotherapy for prostate cancer was associated with rectal cancer in a large database study [35]. Some publications have shown an increased risk of colorectal neoplasia in HIV-positive patients.

Should Colorectal Cancer Be Screened?

Colorectal cancer is a highly treatable disease when diagnosed at an early stage. Early diagnosis in colorectal cancer will reduce mortality and morbidity as well as reduce treatment costs. The way to diagnose colorectal cancer at an early stage is to catch the disease at the asymptomatic stage with screening programs. In screening programs, stool occult blood test, sigmoidoscopy, colonoscopy and imaging methods are used. In the light of this information, early diagnosis is important in order to prevent deaths from colorectal cancer and to apply treatments. Early diagnosis can be achieved with the implementation of high quality and effective screening programs.

Methods Used in Colorectal Cancer Screening Tests in Colorectal Cancer Screening

Faecal Occult Blood Tests

The faecal occult blood test (FOBT) test has some disadvantages. The FOB test is

generally not a good option for screening non-bleeding polyps. The test is more sensitive to cancer than high-grade polyps. In addition, if the FOB test is positive, false positive results should be evaluated [36].

Guaiac-Based Faecal Occult Blood Test:

The presence of hemoglobin in the stool is revealed by the peroxidase reaction [36]. A single test is not sufficient to screen for CRC [37]. Screening should be done with three consecutive tests with two samples in each test [38]. There are varieties of guaiac-based stool occult blood test such as Hemokult, Hemokult 2, Hemokult SENSA (HS) and Hemokult R. HS is more sensitive and less specific for CRC than Hemocult 2 [39]. While the sensitivity of HS in CRC is 64-80%, (40) Hemocult 2 is 25-38%. The specificity of HS is 87–90%, while that of Hemocult 2 is 98–99% [41]. Because of concerns about compliance with annual screening, 2008 guidelines do not recommend screening tests with a sensitivity of less than 50% for cancer [42]. Therefore, only the more sensitive HS test is recommended for screening [439. In the European Journal of Cancer (2012) published and in a study conducted by Anne Kershenbaum et al. Hemaoccult Sensa was used and a rate of 4.2% (+) was found in the FOB test performed on 382,463 patients. This rate could not be repeated in any other center. The positivity rates of these tests are around 15-25%. Therefore, they are not recommended for population-based screening because of the high and unnecessary need for colonoscopy [36].

Immunochemical Tests in Faecal Occult Blood Screening

It is more specific than other FOB tests as they screen only human hemoglobin [36]. These tests are divided into two as qualitative (normal, abnormal) and quantitative. The sensitivity of the immunochemical test decreases with delay in sample processing (degradation of hemoglobin) [44]. The positivity rates of these tests vary between 5-7%. Immunochemical testing is more expensive than other FOB tests, but they outperform others in cost-effectiveness because they have less false positive rate and require less colonoscopy [36]. In an article published in 2011, Janneke A. et al. sought the answer of how we can reduce the need for the number of colonoscopy in countries with limited colonoscopy infrastructure, and investigated with which test they can reduce FOB positivity. If the number of colonoscopy is sufficient, they recommend at least 50ng/ml hemoglobin measurement, if not, they recommend at least 200ng/ml hemoglobin measurement. They stated that they

could only provide these values with immunological quantitative tests. Therefore, the benefit of immunological quantitative testing is to increase the level of hemoglobin measurement in order to further reduce the need for colonoscopy in countries where colonoscopy equipment is relatively scarce. The limit recommended by the World Health Organization (WHO) is 50ng/dl. Studies have shown that there is no significant difference in lesion sensitivity between both hemoglobin levels.

Fecal DNA Test:

Commercially available DNA stool kits contain a DNA panel. All genetic abnormalities associated with CRC have false negatives because they cannot be included in DNA testing. A single test has a sensitivity of 62-100% for CRC, 27-82% for high-grade adenoma,
and 82-100% specificity [45]. This test is expensive [46]. The screening intervals are not clear, in current practice the test is repeated every five years [36].

Double Contrast Barium Enema (DCBE)

In this examination, the intestinal mucosa is plastered with barium, air is introduced into the colon with a rectal catheter, and multiple x-rays are taken under fluoroscopy. Intestinal preparation should be done in patients before the examination. Sedation is usually not done. Patients may feel cramp-like pain during the procedure, but can return to work after the procedure [36]. DCBE can detect half of adenomas larger than 1 cm and 39% of all polyps (46). Retrospective studies show that DCBE misses 15-22% of CRC (47). In the presence of abnormal findings, biopsy or excision should be performed with colonoscopy. False positivity can be caused by residual stool content, air or other mucosal abnormalities. The advantages of DCBE are that the entire colon can be examined and it is a safer method in terms of complications [36].

Sigmoidoscopy

60 cm flexible sigmoidoscopy can reach the splenic flexure. Additional neoplasms may be found in 20% of patients when colonoscopy is performed after polyps found in sigmoidoscopy. Only cases with proximal tumors can be missed in sigmoidoscopy screening [48]. Patient preparation is easier compared to colonoscopy and CT colonography. The procedure can be performed without the need for sedation. The most important complication

is perforation. Sigmoidoscopy perforation rate is 0.08% [54]. While small adenomas can be removed at sigmoidoscopy, adenomas larger than 1 cm are removed at colonoscopy after sigmoidoscopy [41]. Due to technical difficulties, sigmoidoscopy may be prevented from reaching sufficient depth, especially in women and the elderly [49]. They are no longer recommended for screening by the European Union quality criteria.

Colonoscopy

It is advantageous compared to other tests as it allows direct visualization of the colonic mucosa, the possibility of biopsy, and the removal of polyps and local tumors. The American College of Gastroenterology cites colonoscopy as the preferred screening test where it is available [50]. Colonoscopy can detect proximal lesions that can be missed by sigmoidoscopy [51]. Screening with colonoscopy has a greater risk than screening with sigmoidoscopy [48]. The rate of major complications such as perforation and major bleeding is 0.1% [52]. Concomitant diseases, increased age, polypectomy, and less experienced endoscopist increase the risk of perforation [52]. Colonoscopy examination is expensive. Patients are given sedation during the procedure. The patient cannot return to their daily activities after colonoscopy, and they go home accompanied by a person [53]. Although the number of transactions per year is not a quality and reliable measure, it is essential to preserve skills and monitor effective performance. For this reason, it has been determined as a quality standard by the European Union that every endoscopist participating in a recommended colorectal cancer screening program performs at least 300 procedures per year. In addition, since the importance of intubation of the cecum as proof of the completion of the colonoscopy, taking photographs of the procedure was also indicated as an important quality criterion.

Colonography with Computed Tomography (CT Colonography)

In CT Colonography, two and three-dimensional images are obtained by using a large number of thin-section tomography shots. For CT Colonography, patients perform bowel cleansing as in colonoscopy. The reason for this is to avoid false positives [36]. Sedation is not given to the patients during the procedure and patients can return to work after exiting. An intravenous catheter can be inserted during the procedure, with which drugs that relax the smooth muscles of the intestine, such as glucagon, can be administered. Air or carbon dioxide can be given with a catheter placed in the rectum. Images are taken during breath-

hold [36]. Applications in CT Colonography include oral contrast administration, opening the bowel with carbon dioxide, using multidetector-thin section CT scanners, and searching for two- and three-dimensional polyps. CT Colonography should be interpreted by specially trained people [54].

Capsule Endoscopy

In this test, there are two small cameras placed on either side of a capsule. These cameras take images as they pass the column. In this technique, the intestine must be cleaned very well. Any finding requires a biopsy or colonoscopy for polyp excision [55]. In a prospective study, the sensitivity of this method for polyps larger than 6 mm was found to be 64% and specificity 84% [55].

Colorectal Cancer Epidemiology and Current Situation in Colorectal Cancer Screening in Turkey

According to the data of cancer registry centers in 14 provinces in 2016 of the Ministry of Health in Turkey, it ranks third among all cancers with 14.2% in women and third in men with 25.3% in terms of incidence of CRC [2]. Currently, the coverage rate of colorectal scans is between 30-40% and 24.1 diagnosed in our country are in advanced stage. To achieve positive results of colorectal screening, a coverage rate of at least 70% must be achieved.

World Samples of Colorectal Cancer Screening Programmes

COUNTRY	MODALITY TEST	AGE GROUP	SCANNING SPEED
Canada(M)	FOBT every two years	50-74	18 % (2008)
Israel	Annual FOBT	50-74	14 % (2008)
Japan	Annual FOBT	≥ 40 years	17 % (2002)
Korea	Annual FOBT	≥ 50 years	21 % (2008)
Australia	FOBT every two years	55 or 65th birthday. K	38 % (2010)
Crotia	FOBT every two years	50-74	% 20 (2010)
United Kingdom		FOBT every two years	50-75 % 54 (2007)
Finland	**FOBT every two years**	**60-69**	**% 71 (2009)**
France	FOBT every two years	50-74	34 % (2011)
Italy	**FOBT every two years, FS**	**50-69**	**% 48 (2008)**
Scotland	**FOBT every two years**	**50-74**	**% 54 (2010)**
Spain	FOBT every two years	50-69	%34 (2007)
Czech Republic	Annual FOBT or CS	> 55	% 20 (2008)
Germany	**Annual FOBT**	**50-74**	**19%, KS:% 3-4(2009)**
Latvia	Annual FOBT		% 8 (2010)
Poland	Periodic COLONOSCOPY	50-66	(2000-06), < 2 %
USA	**Annual FOBT**	**51-75**	**80 % (2010)**

Table 1 World Examples of Colorectal Cancer Screening Programmes

Colorectal Screening National Program in Our Country Colorectal Cancer Screening Method

Considering the infrastructure and possibilities of our country, the ideal method is screening with the Fecal Occult Blood Test (FOC) to be applied every two years and colonoscopy methods to be performed every 10 years. The Feacal Occult Blood Test should be able to show the presence of hemoglobin in the stool using polyclonal or monoclonal antibodies, and the antigens used in the tests should be sensitive only to human hemoglobin, should not react with hemoglobin of animal origin that can be taken with food, and in this way should not cause false positive results.

Target Population, Start and End Ages of Screening, Screening Frequency

Considering the conditions of our country, the achievable target is population-based screening, which will start at the age of 50 and end at the age of 70 for all men and women. The population to be screened should be repeated at two-year intervals by invitation methods, and screening should be discontinued in men and women aged 70 whose last two tests were negative.

Exceptions

In High Risk and Very High Risk Case Groups

In individuals with a history of colorectal cancer or adenomatous polyps in their first-degree relatives, the same procedures as in the normal population should start from the age of 40, and in individuals with a first-degree relative with colorectal cancer at an early age, the screening procedure should begin 5 years before the age of onset of cancer in their relatives. Except for the general cases stated above, screening and follow-up procedures will be determined by the clinics following the case.

Place

These studies can be carried out together with Community Health Centers, Healthy Life Centers, Cancer Early Diagnosis, Screening and Education Centers (KETEM) and Integration of Family Physicians. These institutions should periodically report the results to the Health Directorates every month to be sent to the Ministry of Health HSGM Cancer Department. Under the responsibility of the Provincial Cancer Control Coordinator, the Provincial Cancer Control Unit is responsible for the coordination, collective registration and follow-up of the Community-Based Screening studies in the Health Directorate.

Distribution the FOB Test

General education on colorectal cancers is given to individuals invited by general practitioners, midwives, nurses and laboratory technicians working in Community Health Centers, Healthy Life Centers, Cancer Early Diagnosis, Screening and Education Centers (KETEM) and Family Medicine. Then, after giving one-to-one demonstration training to the people about the application of the free FOBT kit, the new kit is delivered with an information (application) brochure and the person information is entered into the Colorectal Cancer

Screening Database.

Performing the FOB Test

The FOBT kit, which is distributed free of charge by the general practitioners, midwives, nurses and laboratory technicians working in Community Health Centers, Healthy Life Centers, Cancer Early Diagnosis, Screening and Education Centers (KETEM) and Family Medicine, is administered at home by the people themselves and only the test cassette in the kit is returned to the center where they gave the kit.

Evaluation of the FOBT

Evaluation is made by the family physicians who distribute the kits and the general practitioners, midwives, nurses and laboratory technicians in the centers and are recorded in the database. The person who brings the evaluation tape in the kit is informed about the result and the next process, and necessary guidance is given.

Management to be Applied to Persons with FOB Test (-)

A normal result means that there is no blood in the test sample. Most of the time (about 98 out of 100 people) the result is normal. Some of these people are those who have repeated the test because the previous result was uncertain. A normal result does not guarantee that there is no colorectal cancer or that it will never happen in the future, so the information about the symptoms of colorectal cancer is repeated, the person is given a colorectal cancer information leaflet again and it is said that they will be invited again after 2 years and will be given the opportunity to be screened for colorectal cancer.

Management to be Applied to Persons with FOB Test (+)

An abnormal result indicates that blood has been found in the stool – not a diagnosis of cancer, but means that a colonoscopy should be done. The cause of the abnormal result may be bleeding from the polyps rather than colorectal cancer. It is also possible that it is caused by other diseases such as hemorrhoids (hemorrhoids). If the result is abnormal, to discuss further examination of the large intestine (colon) (colonoscopy) to determine if there is a problem requiring treatment. It should be directed to gastroenterology, general surgery or gastrosurgery services in State Hospitals, Training and Research Hospitals and University

Hospitals. About two out of every 100 people tested have an abnormal result.

Management to be Applied to Persons with Uncertain FOB Test

The uncertain result is that there is no indication that there may be blood in the sample you have taken for the feacal occult blood (FOB) test. An uncertain result doesn't mean you don't have cancer, it just indicates that you need to be tested again. If the result is uncertain, you will be asked to do a feacal occult blood (FOG) test at most two more times. This is necessary because polyps and cancers do not bleed constantly, and it is important to detect blood in the stool. In about four out of every 100 people, the result is uncertain. Normal results are obtained in most of those who repeat the test later.

State Hospitals, Training Hospitals and Universities

The standards related to this issue should be reported to the State, Education and University Hospitals, cooperation should be made in the activities of education and informing the public, the post-transfer treatment of the patients who need advanced treatment should be planned and the feedback should be given in a timely and complete manner.

Introduction

Campaigns should be organized, especially in the written and visual media, in order to promote the screening, inform the public and create demand, spot films should be made by making use of popular artists in Turkey, and these films should be broadcasted at appropriate times.

RESOURCES

1. Globacan 2018 www.globacan.com
2. Sağlık Bakanlığı HSGM Kanser Dairesi Başkanlığı 2016 yılları Türkiye Kanser İstatistikleri
3. Tözün N, Şimşek H, Özkan H, Şimşek İ, Gören A, editörler. Colorectal Polyps and Polyposis Syndromes. Clinical Gastroenterology and Hepatology. Medikal ve Nobel Yayıncılık, 2007: 963- 970.
4. Dolar E, editör. Colorectal Tumors. Nobel ve Güneş Yayınları. 2005: 400-408.
5. Eddy DM. Screening for colorectal cancer. Ann Intern Med. 1990; 113:373.
6. Parkin DM, Pisani, P, Ferlay, J. Global cancer statistics. CA Cancer J Clin 1999; 49:33.
7. Ashktorab H, Nouraie M, Hosseinkhah F. A 50-year review of colorectal cancer in African

Americans: implications for prevention and treatment. Dig Dis Sci 2009; 54:1985.

8. Edwards BK, Ward E, Kohler BA. Annual report to the nation on the status of cancer, 1975-2006, featuring colorectal cancer trends and impact of interventions (risk factors, screening, and treatment) to reduce future rates. Cancer 2010; 116:544.
9. Chan AT, Giovannucci EL. Primary prevention of colorectal cancer. Gastroenterology 2010; 138:2029.
10. Wei EK, Giovannucci E, Wu K. Comparison of risk factors for colon and rectal cancer. Int J Cancer 2004; 108:433.
11. Burt RW, DiSario JA, Cannon-Albright L. Genetics of colon cancer: impact of inheritance on colon cancer risk. Annu Rev Med 1995; 46:371.
12. Colorectal cancer: Epidemiology, risc factors and protective factors. www.uptodate.com.
13. Winawer SJ, Zauber AG, Gerdes H. Risk of colorectal cancer in the families of patients with adenomatous polyps. National Polyp Study Workgroup. N Engl J Med 1996; 334:82.
14. Atkin WS, Morson BC, Cuzick J. Long-term risk of colorectal cancer after excision of rectosigmoid adenomas. N Engl J Med 1992; 326:658.
15. Molecular genetics of colorectal cancer. www.uptodate.com.
16. Ekbom A, Helmick C, Zack M, Adami HO. Ulcerative colitis and colorectal cancer. A population-based study. N Engl J Med 1990; 323:1228.
17. Brentnall TA, Haggitt RC, Rabinovitch PS. Risk and natural history of colonic neoplasia in patients with primary sclerosing cholangitis and ulcerative colitis. Gastroenterology 1996; 110:331.
18. Velayos FS, Loftus EV, Jr Jess T. Predictive and protective factors associated with colorectal cancer in ulcerative colitis: A case-control study. Gastroenterology 2006; 130:1941.
19. Rutter M, Saunders B, Wilkinson K. Severity of inflammation is a risk factor for colorectal neoplasia in ulcerative colitis. Gastroenterology 2004; 126:451.
20. Gillen CD, Walmsley RS, Prior P. Ulcerative colitis and Crohn's disease: a comparison of the colorectal cancer risk in extensive colitis. Gut 1994; 35:1590.
21. Erlinger TP, Platz EA, Rifai N, Helzlsouer KJ. C-reactive protein and the risk of incident colorectal cancer. JAMA 2004; 291:585.
22. Zhang SM, Buring JE, Lee IM. C-reactive protein levels are not associated with increased risk for colorectal cancer in women. Ann Intern Med 2005; 142:425.
23. He J, Stram DO, Kolonel LN. The association of diabetes with colorectal cancer risk: the Multiethnic Cohort. Br J Cancer 2010; 103:120.
24. Larsson SC, Orsini N, Wolk A. Diabetes mellitus and risk of colorectal cancer: a meta-analysis. J Natl Cancer Inst 2005; 97:1679.

25. Giovannucci E, Colditz GA, Stampfer MJ. A meta-analysis of cholecystectomy and risk of colorectal cancer. Gastroenterology 1993; 105:130.
26. Longnecker MP, Orza MJ, Adams ME. A meta-analysis of alcoholic beverage consumption in relation to risk of colorectal cancer. Cancer Causes Control 1990; 1:59.
27. Pedersen A, Johansen C, Grønbaek M. Relations between amount and type of alcohol and colon and rectal cancer in a Danish population based cohort study. Gut 2003; 52:861.
28. Shimizu N, Nagata C, Shimizu H. Height, weight, and alcohol consumption in relation to the risk of colorectal cancer in Japan: a prospective study. Br J Cancer 2003; 88:1038.
29. Ye W, Romelsjö A, Augustsson K. No excess risk of colorectal cancer among alcoholics followed for up to 25 years. Br J Cancer 2003; 88:1044.
30. Chan AO, Jim MH, Lam KF. Prevalence of colorectal neoplasm among patients with newly diagnosed coronary artery disease. JAMA 2007; 298:1412.
31. Botteri, E, Iodice, S, Raimondi, S. Cigarette smoking and adenomatous polyps: a meta-analysis. Gastroenterology 2008; 134:388.
32. Stewart, M, Macrae, FA, Williams, CB. Neoplasia and ureterosigmoidostomy: a colonoscopy survey. Br J Surg 1982; 69:414.
33. Cross AJ, Ferrucci LM, Risch A. A large prospective study of meat consumption and colorectal cancer risk: an investigation of potential mechanisms underlying this association. Cancer Res 2010; 70:2406.
34. Thompson D, Easton DF, Breast Cancer Linkage Consortium. Cancer Incidence in BRCA1 mutation carriers. J Natl Cancer Inst 2002; 94:1358.
35. Baxter NN, Tepper JE, Durham SB. Increased risk of rectal cancer after prostate radiation: a population-based study. Gastroenterology 2005; 128:819.
36. Tests for screening for colorectal cancer: Stool tests, radiologic imaging and endoscopy. www.uptodate.com.
37. Sox HC. Office-based testing for fecal occult blood: do only in case of emergency. Ann Intern Med 2005; 142:146.
38. Nadel MR, Shapiro JA, Klabunde CN. A national survey of primary care physicians' methods for screening for fecal occult blood. Ann Intern Med 2005; 142:86.
39. Pignone M, Campbell MK, Carr C, Phillips C. Meta-analysis of dietary restriction during fecal occult blood testing. Eff Clin Pract 2001; 4:150.
40. Allison JE, Sakoda LC, Levin TR. Screening for colorectal neoplasms with new fecal occult blood tests: update on performance characteristics. J Natl Cancer Inst 2007; 99:1462.
41. Whitlock EP, Lin JS, Liles E. Screening for colorectal cancer: a targeted, updated systematic review for the U.S. Preventive Services Task Force. Ann Intern Med 2008; 149:638.
42. Levin B, Lieberman DA, McFarland B. Screening and surveillance for the early detection of

colorectal cancer and adenomatous polyps, 2008: a joint guideline from the American Cancer Society, the US Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology. CA Cancer J Clin 2008; 58:130.

43. U.S. Preventive Services Task Force. Screening for colorectal cancer: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med 2008; 149:627.
44. Van Rossum LG, van Rijn AF, van Oijen MG. False negative fecal occult blood tests due to delayed sample return in colorectal cancer screening. Int J Cancer 2009; 125:746.
45. Ahlquist DA, Sargent DJ, Loprinzi CL. Stool DNA and occult blood testing for screen detection of colorectal neoplasia. Ann Intern Med 2008; 149:441.
46. Winawer SJ, Stewart ET, Zauber AG. A comparison of colonoscopy and double-contrast barium enema for surveillance after polypectomy. National Polyp Study Work Group. N Engl J Med 2000; 342:1766.
47. Toma J, Paszat LF, Gunraj N, Rabeneck L. Rates of new or missed colorectal cancer after barium enema and their risk factors: a population-based study. Am J Gastroenterol 2008; 103:3142.
48. Gatto NM, Frucht H, Sundararajan V. Risk of perforation after colonoscopy and sigmoidoscopy: a population-based study. J Natl Cancer Inst 2003; 95:230.
49. Walter LC, de Garmo P, Covinsky KE. Association of older age and female sex with inadequate reach of screening flexible sigmoidoscopy. Am J Med 2004; 116:174.
50. ex DK, Johnson DA, Anderson JC. American College of Gastroenterology guidelines for colorectal cancer screening 2009 [corrected]. Am J Gastroenterol 2009; 104:739.
51. Imperiale TF, Wagner DR, Lin CY. Risk of advanced proximal neoplasms in asymptomatic adults according to the distal colorectal findings. N Engl J Med 2000; 343:169.
52. Warren JL, Klabunde CN, Mariotto AB. Adverse events after outpatient colonoscopy in the Medicare population. Ann Intern Med 2009; 150:849.
53. Bowel preparation of colonoscopy. www.uptodate.com.
54. Johnson, CD, Chen, MH, Toledano, AY. Accuracy of CT colonography for detection of large adenomas and cancers. N Engl J Med 2008; 359:1207.
55. Van Gossum A, Munoz-Navas M, Navas MM. Capsule endoscopy versus colonoscopy for the detection of polyps and cancer. N Engl J Med 2009; 361:264.

CHAPTER 5

THIRD PROTECTION

5.1. Post Screening Diagnosis and Treatment Centers

Scanning and post-scan diagnosis are interrelated processes. Early diagnosis of breast, cervix and colorectal cancers through community-based screening programs conducted in line with National Screening Standards, providing necessary medical referrals to patients diagnosed with cancer and referral to treatment centers, patient follow-up and evaluation, and providing social, mental and medical support as much as possible constitute an important part of cancer control. Directing the patient to the right centers for diagnosis and the quality of the diagnosis-treatment service have an important place in the evaluation of the quality of the screening program.

In our country, in our centers providing primary health care services (TSM, SHM, KETEM, ASM, Mobile Mammography tools) our citizens, who are screened for breast cancer, cervical cancer and colorectal cancer, after screening, diagnosis and treatment centers with advanced technology to which suspicious cases can be referred have been identified. As of 2021, we have 173 centers where referrals are made after scanning.

Mandatory personnel and technical requirements in post-screening diagnosis centers for breast, cervix and colorectal cancer:

Breast cancer

1. Radiology Specialist
2. Pathology Specialist
3. General surgery specialist
4. Mammography device with which additional shots such as spot magnification and compression can be taken
    a. Tru-cut thick needle biopsy
    b. Fine needle biopsy
    c. Wire marking with US accompaniment
5. High resolution US device

Optional Items

1. Digital mammography device with tomosynthesis feature
2. MR device with breast MR software

3. Stereotactic breast biopsy
4. Wire marking with mammography accompaniment

Cervical cancer

1. Gynecologist
2. Pathology Specialist
3. Colposcopy device that can print picture

Colorectal Cancer

1. General Surgery and/or Gastroenterology Specialist
2. Pathology Specialist
3. Colonoscopy device that can print pictures, in an environment where anesthesia can be given, conditions for polypectomy can be performed

Increasing the quality and duration of life in screening programs is possible with early diagnosis. How a "positive" case was diagnosed, when and how it was treated have been defined by European Quality Standards. **Some of the standards set for diagnosis and treatment are listed below:**

For Breast Cancers:

- Breast cancer diagnosis rate with needle biopsies (FNAB, Vacuum or Core biopsy): ≥ 90%
- Inadequate result rate in needle biopsies: <20%
- Need for reoperation after incomplete excision: 10%
- Time taken to make the operation decision and take it into operation: 15 working days

For Cervix Cancers:

Since the incidence of cervical cancer differs from country to country, studies have not been able to show precise quality criteria as in breast cancer screening. However, the following performance indicators should be evaluated annually in national screening programs.

- Scan coverage should be at least 70%
- For lesions of CIN II and above, HPV test sensitivity should be at least 90% and specificity should be at least 98% of the reference test (HC II).

- Ratio of cancer cases detected by screening to all cancer cases
- Proportion of women called for retest
- Referral rate for colposcopy
- Participation rate in colposcopy
- Proportion of women with lesions histologically confirmed by colposcopy to all of those who underwent colposcopy
- Proportion of cancer among those with abnormal results

For Colorectal Cancers:

- Sedation
- Follow-up of patients after sedation
- Antibiotic prophylaxis
- Anticoagulant monitoring
- Colon cleansing
- Endoscopic evaluation of colorectal abnormalities;
- Endoscopic removal of lesions (both high and low risk);
- Marking of high-risk lesions;
- Also management of high-risk lesions and equipment.

Minimum Requirements for Endoscopic Reporting

- Determining the procedure by which the lesion was obtained
- Patient / client information
- Endoscopy type (FS or KS)
- Team (endoscopist and auxiliary staff)
- Purpose of the procedure
- Primary scan
- First scan or next scan
- Elapsed primary scan procedure interval (if any)
- Endoscopic examination range mentioned above

Evaluation of Abnormal Findings

- After positive screening test
- After positive symptomatic test

Surveillance for Reassessment of Abnormal

- Findings
- Range of last endoscopic procedure and type of procedure
- Preparation, insufflation and sedation
- Bowel cleansing regimen
- Insufflation gas (air or CO2)
- Type of anesthesia and substances used
- Visualization of the end of the cecum
- Intubation time (time at the beginning of the procedure, time to the end of the cecum)

The reasons for the missing examination should be determined.

As can be seen from these features, diagnosis and screening are a whole, if both are carried out properly, an effective screening program can be applied.

5.2. Diagnosis, Clinical Stating and Treatment Methods in Breast Cancer Which is One of The Most Common Cancers

In recent years, great progress has been made in the diagnosis and treatment of breast cancer, which is the most common breast cancer in women in our country. For this reason, the importance given to screening programs has increased even more as our women are aware of the developments in diagnosis and treatment in our screening programs.

5.2.1. Diagnosis in Breast Cancer

5.2.1.1 History and Physical Examination

We recommend that women with an average risk for breast cancer should have breast examinations at the clinic every 2-3 years from the age of twenty and every year after the age of forty, and mammography should be added to this once a year from the age of 40 [1]. There are some important points to keep in mind before starting the examination. Among the

lesions to be detected by examination, benign ones are more common than malignant ones. The presence or absence of risk factors should not preclude investigation of a breast-related complaint. All women are at risk for breast cancer, and it should not be forgotten that all applications should be investigated until the diagnosis is sure.

Medical history

Like all system and organ examinations, breast examination begins with a detailed anamnesis. Age is the most important risk factor for breast cancer, and diagnostic algorithms differ according to age. The patient's history and complaints of all systems, including the breast, should be questioned. In addition, current diseases, medications, allergic status and family history should be known. With a well taken anamnesis, an idea about the underlying causes of the symptoms can be obtained and physical findings to be considered can be predicted.

The most common complaints in women who apply to breast outpatient clinics other than routine controls are breast pain, mass and nipple discharge. In women who do not regularly participate in the mammographic screening program, the most common manifestation of breast cancer is the masses noticed in the breast. In a patient who presents with the complaint of a breast mass, first of all, when and how the mass was noticed and whether there was an increase in its size should be questioned. While the size of malignant masses may increase over time, the size of benign cysts may decrease in the follicular phase of the menstrual cycle. During inspection, the appearance, skin change, size and symmetry of the breasts are checked. If the mass in the breast is painful, its localization, duration, whether it requires analgesics, and its relationship with daily activity and menstrual cycle are questioned. If there is a complaint of discharge from the nipple, it is investigated whether it is unilateral, spontaneous, bloody or serous. It should not be forgotten that traumas to the breast can lead to fat necrosis and hematoma. However, even if there is a history of trauma to the breast, all breast masses should be illuminated with algorithms.

Another important point to be considered when taking anamnesis from a patient undergoing breast examination is whether the patient has known risk factors for breast cancer. If there is a relative diagnosed with breast cancer in the family, age at diagnosis, whether they are male and whether it was bilateral should be questioned. Menarche,

menopause, age at first birth, number of pregnancies and live births, breastfeeding duration, history of oral contraceptive and hormone replacement therapy, alcohol and cigarette use, previous breast biopsy history and results should be learned, and body mass index should be calculated by learning height and weight. In premenopausal women, the last menstrual period, duration and order of menses are questioned.

Physical Examination

In breast examination, it is necessary to evaluate both breasts, axilla, supracalvicular and infracalvicular regions. The patient is taken to a bright examination room with a nurse. If possible, there should be a separate isolated area where the patient can be prepared for examination. If the patient comes with a complaint in the breast, the examination is started with the other breast. After the examination, imaging studies and, if necessary, biopsy should be recommended. Pain, hematoma or skin edema caused by cutting needle biopsy cause changes in examination findings.

Like all examinations, breast examination begins with inspection. The patient's waist should be exposed in such a way as to allow inspection and examination. The examination is done in 3 ways with the patient standing, sitting and lying down. While standing, she stands in front of the doctor with her arms hanging down. The patient is then asked to raise their arms above their head so that the lower quadrants of the breasts are better visible. Then the patient puts her hands on their waist and presses her pectoral muscles to contract. In this way, retraction areas, if any, are revealed in the breast. During inspection, breast asymmetry, conspicuous swelling, thickening of the breast skin, edema, cellulitis, ulceration, small pittings (orange peel appearance), erythematous and eczematous changes are observed carefully. Superficial mammary tumors can cause retraction of the breast skin, differentiation in the contours of the breast, and visible lumps. Deeper tumors may involve the Cooper ligament of the breast and cause retraction. Edema on the skin of the breast may be due to local cellulitis or abscess, or it may be a sign of inflammatory breast cancer in which the skin lymphatics are involved. In inflammatory breast cancer, edema involving more than 1/3 of the breast, redness and sometimes an increase in temperature are observed. The orange peel image also indicates that the breast cancer has spread to the lymphatics in the skin of the breast. It is important to evaluate the nipples in terms of asymmetry, inversion, retraction and nipple discharge. The nipples are expected to be symmetrical and slightly outward.

Particular attention should be paid to findings such as redness, crusting, flaking in the nipple and areola area. These symptoms may be a sign of Paget's disease of the nipple. In patients with nipple discharge, the discharge should be controlled by gently pressing from the periphery towards the nipple.

The breast should be palpated bimanually while the patient is in a sitting position. While one hand gently supports the patient's breast from below, palpation is made using the inner surfaces of the pulps of the three fingers of the other hand. When the breast tissue is compressed between two fingers, a false mass sensation can be taken. In sitting position, masses close to the tail of the nipple can be palpated more easily.

Examination of regional lymph nodes is also done in a sitting position. During this examination, axilla, supraclavicular, infraclavicular and cervical lymph nodes are checked. The hand or arm on the side to be examined is held with the hand that will not perform the examination, and the weight is asked to be placed on the doctor's hand. In this way, the lattissumus dorsi and pectoral muscles relax and the base of the axilla can be reached. The right axilla is examined with the left hand, and the left axilla with the right hand. The axillary tissue is compressed between the chest wall and the fingers, and a sweeping motion is made from the base of the axilla down to its base. In the meantime, skin lesions, small abrasions and infected lesions on the arms, fingers and nails that may cause axillary lymphadenopathy should be evaluated. Estimated size, shape, number, firmness, tenderness, and mobility of palpable lymph nodes should be recorded. Lymph nodes smaller than one centimeter, soft and mobile, are usually reactive lymph nodes and do not have a suspicion of serious metastatic lymph nodes. Palpation of lymph nodes in the supraclavicular area is an important clinical condition that requires further observation and investigation.

Then, the patient is laid down with a pillow under their back and asked to put their hands above their head. Thus, the breast tissue spreads over the pectoral muscle and the examination becomes easier. In order to straighten and loosen the outer quadrants of the breast, it is requested to turn slightly to the opposite side while lying down. Since the breast tissue extends towards the axillary tail, it is necessary to make sure that all breast tissue is examined. The examination performed up to the clavicle above, the sternal border medially, the mid-axillary line laterally, and the costal arch below, usually covers the entire breast tissue. During palpation, the pulps of three fingers, except the thumb and little finger, are

used. Both breasts are examined in 3 ways from the nipple to the periphery by drawing round circular rings (circular), from the periphery to the nipple (radial), and from the top-down and the bottom up. Palpation is applied. First, palpation is made at the superficial level and then into deeper tissues. During palpation, the other hand supports the breast. If the physician cannot palpate a mass that the patient reported having noticed during self-examination, the patient is asked to find this mass and this area is re-examined.

All masses and pathological findings detected during the examination should be recorded. The quadrant where the masses are located and the distance to the nipple are noted. If necessary, localization can be specified clockwise based on the areola. The estimated size of the masses, hard or soft consistency, and fixed or mobile in the surrounding tissues are important characteristics that should be recorded. The irregular and nodular breast structure that can be seen in pre-menopausal women can cause confusion in palpation, but this situation is often not pathological. Complete and accurate documentation facilitates the follow-up of related lesions in subsequent examinations.

RESOURCES

1. *Niell BL, Freer PE, Weinfurtner RJ, Arleo EK, Drukteinis JS. Screening for breast cancer. Radiol Clin North Am. 2017;55(6):1145-1162.*

5.2.1.2. Diagnostic Radiological Methods in Breast Cancer

Imaging of the breast has an extremely important place in the screening, diagnosis, prognosis, treatment selection, and follow-up of breast cancer. Diagnostic examination is performed in patients with symptoms such as palpable mass, nipple discharge, skin changes, nipple retraction, or breast pain.

Diagnostic Mammography (MG): It is the examination performed to diagnose patients with complaints. In MG, images are taken in two basic positions (mediolateral oblique and craniocaudal) for each breast as standard. In total, the dose taken for 4 films is 3-4 mSv on average. Since this is as much as the radiation dose received in 1 year in nature, it is unnecessary to be afraid of the radiation dose taken from MG for diagnostic purposes. Correct position and compression are very important for a quality mammogram image. A good compression also affects the radiation dose that the breast will receive. Additional images (spot compression, magnified spot compression, tangential, etc.) can be taken in

diagnostic MG when necessary. In case of suspected pathological findings, a biopsy should be performed with imaging guidance. Apart from conventional (traditional) MG, new techniques used in imaging such as digital mammography (DM), digital mammography tomosynthesis (DMT), and contrast-enhanced spectral mammography (CSM) have been developed.

DM is more sensitive than traditional MG in women with dense breast tissue. The Turkish Society of Radiology states in the Breast Cancer Screening Guide that DM should be preferred first [1].

Digital Mammography Tomosynthesis: Also known as 3D MG, it allows reconstruction of the images obtained by moving the x-ray tube with small angles (15-50 degrees), obtaining thin cross-sectional images, and examining the lesions in three dimensions. DMT increases sensitivity by preventing tissue superposition in women with dense breast tissue. Studies have shown that DMT reduces recall and unnecessary biopsy rates in women with dense breasts and causes at least a 30% increase in cancer detection [2]. Therefore, DMT should be preferred in women under the age of 50, in the pre/perimenopausal period, and in women with heterogeneously dense or dense breasts. The total dose given for a single position is equal to DM.

Contrast-Enhanced Spectral Mammography: First studies started in the early 2000s. In CSM, breast imaging is performed with DM or DMT after intravenous contrast material administration. In recent meta-analyses, it has been reported that although its sensitivity (98%) is high, its specificity (38%) is low [3]. It can be used as a substitute for MRI in patients with contraindications to MRI or in claustrophobic patients, but cannot replace MRI with contrast [2].

Ultrasonography: US should not be used as a primary screening method in place of MG alone. The purpose of diagnostic US is to investigate the ultrasonographic findings of a palpable mass or some abnormal findings on mammography. In addition, some lesions in the dense breast may be missed in MG, so the US can be used as a complement to mammographic screening in dense breasts. The US should be the first modality of choice in symptomatic patients under the age of 40. During ultrasonography, the axilla should also be evaluated and suspicious LAPs should be stated as numbers.

US examination of the breast for diagnostic and/or interventional purposes should be

performed in the following cases [1]:

1. Evaluation and characterization of palpable masses and other breast-related complaints and/or clinical findings

2. Evaluation of suspected or obvious abnormalities detected by mammography (MG), magnetic resonance imaging (MRI), or other modalities

3. In patients under 30 years of age who are not at high risk for developing breast cancer,

4. Evaluation of suspicious examination findings detected in pregnant or lactating women as the first step

5. Evaluation of problems with breast implants

6. Guiding breast biopsy or other interventional procedures

7. Evaluation of the male breast

8. Evaluation of pathological lymph nodes in the axilla and biopsy guidance in the presence of suspicious findings

Doppler US: It shows the vascular characteristics of mass lesions detected in the breast by ultrasonography. It has an important role in the differentiation of solid tissue and debris, especially in complex cysts. If vascularization is observed in the solid area, a US-guided biopsy is recommended.

US-Elastography: Elastography makes color-coding or hardness grading according to the stiffness and flexibility of tissues. The incidence of malignancy is high in patients with high tissue stiffness and it helps to evaluate suspicious lesions.

Magnetic Resonance Imaging: The breast should not be taken except for MRI indications and should not be the first choice. It should be suggested and evaluated by a breast radiologist as a problem solver in cases that cannot be decided by MG and US [1].

Breast MRI Indications:

1. In the pre-operative local evaluation of the tumor in necessary cases;

2. In cases where conventional imaging and clinic are not sufficient

3. In the investigation of occult breast tumors (in cases not found by MG and US)
4. In the distinction between scar and recurrence in intermediate cases for whom a biopsy decision could not be made with conventional imaging in the follow-up after breast-conserving surgery (BCS)
5. In the follow-up of the cases that are planned to be applied BCS in the locally advanced stage (in the cases that cannot be resolved by MG and US)
6. In cases with suspected rupture of the breast prosthesis (non-contrast MRI may be sufficient)
7. In addition to MG and US in the case of breast prosthesis and symptoms such as palpable mass, etc.
8. Investigation of response to treatment and spread of residual malignancy after chemotherapy and/or radiotherapy,
9. In the evaluation of residual disease in patients with positive or near surgical margins

MRI has high sensitivity but low specificity. However, due to its high sensitivity in DCIS tumors in recent studies, it is also recommended to be used in screening in high-risk groups [1].

RESOURCES

1. *Breast Cancer Screening Guideline, Turkish Radiology Association, TRD Competency Board of Directors, Guidelines and Standards Committeei, 2011*
2. *Strand F, Zackrisson S. Breast cancer imaging-A rapidly evolving discipline. The Breast 2019; 46:58-63.*
3. *Tagliafico AS, Bignotti B, Rossi F, et al. Diagnostic performance of contrast-enhanced spectral mammography: systematic review and meta-analysis. Breast 2016; 28:13–9.*

5.2.1.3. Biopsy Methods in Breast Cancer

Today, open surgical biopsies have been replaced by easily applicable, inexpensive, percutaneous, non-invasive, reliable biopsy techniques, and have become the gold standard for tissue diagnosis [1,2]. 4 methods are used to biopsy a defined lesion in the breast:

1. Fine needle aspiration biopsy (FNAB),

2. Core needle biopsy,
3. Vacuum assisted biopsy (VAB),

4-. Open surgical biopsy

Minimally invasive biopsy techniques performed percutaneously are extremely successful, especially when accompanied by imaging methods.

As an imaging method, the US is the first preferred method because it does not contain radiation, is a quick, easily accessible and inexpensive method.

Stereotactic breast biopsy is performed under MG guidance. It is used for lesions that are not palpable, visualized by MG but not by the US. After biopsies due to microcalcification, radiographs of the specimen should be performed before the tissues are fixed (4).

An MRI-guided breast biopsy is used only in lesions that cannot be detected by US and MG, but is an expensive and difficult technique [1-4].

Breast interventional procedures are performed for diagnostic or therapeutic purposes.

Diagnostic procedures are needle-wire marking, fine-needle aspiration biopsy (FNAB), thick-needle core biopsy, and vacuum biopsy methods.

Diagnostic/treatment methods are cyst aspiration and abscess drainage, and marker placement on the lesion before neoadjuvant chemotherapy application.

Before interventional procedures: Before making a biopsy decision on a lesion detected in the breast, the adequacy of the imaging should be evaluated and additional investigations should be completed if necessary. The possibility of malignancy of the lesion revealed by mammography/US and/or MRI should be evaluated and the necessity of biopsy in suspicious lesions should be stated in the report. It should also be noted which imaging method the lesion can be seen better and which approach will be appropriate in terms of application. Allergy history (local anesthetic, skin antiseptic), and use of drugs that will facilitate bleeding (aspirin, anticoagulants) should be questioned while planning the appointment before the procedure. In non-emergency situations, it is recommended to discontinue the use of anticoagulants for about 5 days before the procedure [1,5].

Indications for US-Guided Interventional Procedures:

Symptomatic cysts

Lesions that cannot be differentiated from complicated cysts and solids

Diagnostic aspiration or therapeutic drainage in suspected abscess

Complex cystic-solid masses Suspicious areas of calcification visible on the US.

Some BIRADS 3 cases (such as high risk, the fact that it is difficult to follow-up)

Lesion marking (pre-NACT marker placement/pre-surgical lesion marking) Suspicious

axillary lymph node (by FNAB or core needle biopsy)

Indications for Stereotactic Interventional Procedures:

BIRADS 4 and BIRADS 5 lesions seen on mammography

Some BIRADS 3 cases (such as high risk, the fact that it is

difficult to follow up) Lesion marking (can be used as an

alternative to standard mammography)

Fine-Needle Aspiration Biopsy (FNAB): The insufficiency of the sample taken in fine-needle aspiration biopsies (37%) and the high false-negative rate (31%) limited its use. With FNAB, a benign-malignant distinction can be made and rapid results can be obtained. However, while in situ or invasive cancer cannot be differentiated with this biopsy, it is not possible to evaluate prognostic and predictive factors such as ER/PR, aneuploidy, HER-2, histological grade with immunohistochemical studies. Surgery should not be planned for patients with only an FNAB result [2].

Core Needle Biopsy (CORE BIOPSY-CB): It has become standard in all breast lesions detected by palpation and visualized by the US, MG and MRI. It was first used in 1993 after the publication of the work of Parker et al., and it has become increasingly common. Biopsy should be performed with whichever method the lesion can be visualized better. The stereotactic method can be applied in units with a prone table or with units added to mammography. It is very effective in lesions seen in MG, especially in calcification sampling. As the needle size increases in CB, the accuracy of diagnosis increases. By using 14G -16G long shot (2 cm) needles, sufficient tissue is obtained with the fully automatic gun

system and in situ and invasive differentiation can be made in malignant lesions. With this biopsy, the parameters that determine the prognosis and treatment are determined in advance, the treatment is planned and surgical treatment is performed in one step. In patients who will undergo Breast Conserving Surgery (BCS), better cosmetic results are achieved as the breast is not deformed much after lumpectomy. For benign lesions, open surgical biopsy is avoided. The rate of insufficient material is low (2-4%). In US-guided CB, the false-negative rate is 0-9% due to the tissue not being taken from the right place. The factors that affect the tissue not being taken from the right place can be listed as the localization of the lesion, its size, its mobility, the dense structure of the breast, the experience of the doctor, and the tolerance of the patient's procedure. The procedure should be performed with caution in patients with breast prostheses. In patients with bleeding diathesis or using anticoagulants, preparation should be made in consultation with the doctor who prescribed the drug, and compression should be applied after the biopsy. After the core biopsy, it is recommended that the patient is given analgesics, a bra that wraps the breast and shortens its movement, and does not do any heavy work and sports for 24 hours [2-7].

Vacuum Assisted Biopsy (VDB): It is a method that can be applied especially in cases where large sampling is required such as atypical ductal hyperplasia (ADH) and ductal carcinoma in situ (DCIS). In the VDB system, there is a 360-degree rotating cutting tip connected to the negative pressure system, which is used to take biopsies from the lesion many times, and 6 biopsies can be taken in one round. It can be applied with US, MG and MRI. While 10G-11G is used to take a biopsy, 7G or 8G needles can be used where complete removal of the lesion is aimed. At the end of the VDB procedure, the location of the lesion should be marked with a clip or carbon marker, and the location of the marking should be confirmed by MG taken immediately after the procedure (CC and ML) [2,4].

Interventional procedures in the breast should be performed and reported by radiologists. The success of the examination depends on the fact that it is performed by people who are experienced in breast imaging. In the pathological diagnosis, a thick needle biopsy or VDB should be performed, preferably with US guidance. FNAB can be performed especially in superficial lesions close to the chest wall or in the presence of a prosthesis. Fine-needle aspiration biopsy may be preferred for suspicious axillary lymph node sampling, but thick-needle biopsy is recommended for lymph nodes distant from vascular structures. During the process, images should be recorded and stored in the archive. Post-biopsy imaging findings

and pathological results should be compared and the compatibility between them should be questioned [1-5].

Pre-Excision Marking: The aim is to mark the non-palpable lesions and then remove them under the guidance of this mark. In this way, good cosmetic results are obtained. Marking can be done under the guidance of mammography, US and MRI. It is preferred that all lesions detectable by the US are marked with USG. US-guided marking is fast, practical, and comfortable for the physician and the patient. Owing to the simultaneous display, the process can be performed in a controlled and error-free manner. The success rate is higher than mammography guidance. In mammography-guided markings, it is essential to approach the lesion from the shortest possible distance. The position to be marked is determined accordingly [1-5].

Roll Biopsy: A multidisciplinary working environment and special equipment are required for ROLL (radionuclide guided occult lesion localization). In this method, colloidal albumin labeled with Tc 99 m is injected directly into the lesion and the location of the lesion is determined with a gamma probe during the operation. Since the surgeon will make an incision directly over the lesion, it is possible to end the procedure by removing less tissue [2,8].

Open Surgical Biopsy: Until the 1980s, the only surgical biopsy was performed in the histopathological diagnosis of breast lesions. The indication of core biopsies has decreased considerably due to the fact that the results of open surgical biopsies are equivalent to the results of open surgical biopsies and the chance of BCS and SLNB of the patient is reduced due to open surgical biopsies. However, an open surgical biopsy can be performed in lesions located close to the chest wall or nipple, lesions close to the breast implant, very small microcalcifications that are difficult to stereotactically mark or biopsy due to their localization, lesions with ALH, LCIS as a result of CB, and complex radiological lesions such as radial scars.

Wire-Guided Surgical Biopsies: In cases where stereotactic core biopsies are insufficient or technically impossible for the diagnosis of microcalcifications, the lesion marked with wire by the radiologist under US or MG guidance is removed by the surgeon [9,10].

In conclusion, diagnostic core biopsy should be the first choice in breast lesions today.

Performing this procedure with imaging increases its reliability. Today, percutaneous minimally invasive breast biopsies performed with US, MG, or MRI have become the gold standard for tissue diagnosis. As an imaging method, a cheap and simple method should be preferred, which has a high chance of obtaining sufficient samples and displays the lesion well.

The cosmetic results of the core biopsy are very good and facilitate the application of BCS and SLNB. Surgical biopsies should not be used for diagnostic purposes unless it is necessary.

RESOURCES

1. Holloway CM, Gagliardi AR. Percutaneous needle biopsy for breast diagnosis: how do surgeon decide? Ann Surg Oncol 2009 Jun;16(6):1629-36.

2. O'Flynn EAM, Wilson ARM, Michell MJ. Image-guided breast biopsy: state-of-the-art. Clin Radiol 2010 65:259-270

3. Calhoun BC, Collins LC. Recommendations for excision following core needle biopsy of the breast: a contemporary evaluation of the literature. 2016: 68;138-151.

4. Huang ML, Adrada BE, Candelaria R et al. Stereotactic breast biopsy:pitfalls and pearls. Tech Vasc Int Radiol 2013: 17;32-39.

5.https://www.turkrad.org.tr/assets/pdfDocs/Meme-Girisimsel-Islemler-Standartlari-2018.pdf

6. Calhoun BC. Core needle biopsy of the breast. Surg Pathol 2018: 11;1-16.

7. Neal L, Sandhu NP, Hieken TJ at al. Diagnosis and management of benign, atypical and indeterminate breast lesions detected on core needle biopsy. Mayo Clin Proc 2014:89;(4): 536-547.

8. Gül Esen, Görüntüleme Eşliğinde Girişimsel Meme İşlemleri Teknik ve Uygun Yöntem Seçimi, Turkiye Klinikleri J Radiol Special Topics 2017, 10(3):e259-70

9.Hanna WC, Demyttenaaere SV, Ferri LE et al. The use of stereotactic excisional biopsy in the management of invasive breast cancer. World J Surg 2005: 29; 1490-94.

10.Liu WH, Teng GJ, Jiang J. Mammography and breast localization for interventionalist. Tevh Vasc Int Radiol 2014; 17:10-5.Liberman L, Sama MP. Cost-effectiveness of stereotactic gauge directional vacuum-assisted breast biopsy. AJR 2000; 175:53-8.

5.2.2. Clinical Staging in Breast Cancer

Clinical staging should be performed before starting treatment in patients diagnosed with breast cancer. Tumor, TNM (Tumor Nodule Metastasis) staging system, first identified by the American Joint Committee on Cancer (AJCC) in 1959, is a system that helps in deciding the prognosis and treatment of the disease. Version 8 of the AJCC, published in January 2018, divides staging for breast cancer into anatomical (clinical) and prognostic (pathological) [1]. Anatomical staging, also known as clinical staging, is performed based on data obtained from clinical, radiological and, if necessary, biopsy materials in patients who have not yet undergone surgery. In prognostic staging, pathological information is added to clinical staging. In addition, there are ypTNM staging systems used in patients receiving neoadjuvant therapy and rTNM staging systems used in patients with recurrence. In this section, the clinical staging system will be discussed. Tumor, Nodule, Metastasis (TNM) used in the clinical staging system refers to;

T: indicates primary invasive tumor size, determined by tumor size obtained on physical examination or radiological imaging (MR, US, or MG).

N: Indicates the presence of regional lymph node

involvement. M: Indicates the presence of distant

metastases.

TNM definitions and clinical staging system are shown in Table-1 and Table-2.

Table- 1 TNM descriptions

Tumor stage (T)	
Tx	The primary tumor cannot be evaluated.
T0	There is no evidence of primary tumor.
Tis	DCIS or DCIS-related Paget's disease of the nipple

T1	The greatest diameter of the tumor ≤ 20 mm T1a >1 mm tumor diameter ≤ 5 mm T1b >5 mm tumor diameter ≤10 mm T1c >10 mm tumor diameter ≤ 20 mm
T2	>20 mm tumor diameter ≤ 50 mm
T3	tumor diameter >50 mm
T4	Chest wall and/or skin (ulceration or skin nodules) involvement*
	T4a: chest wall involvement
	T4b: ulceration, satellite nodules, or edema exist on skin *(including 'peau d'orange'*)
	T4c : T4a +T4b
	T4d: inflammatory breast carcinoma
Lymph Node Stage (N)	
Nx	Regional lymph nodes cannot be evaluated (previously removed or no physical examination information)
N0	No regional lymph node metastases
N1	There is axillary lymph node metastasis
	cN1mi – there is micrometastasis (>0,2 mm < 2,0 mm

N2	There is clinically fixed or conglomerated axillary lymph node metastasis or clinical metastasis in ipsilateral internal mammary lymph nodes.
	N2a: there is metastasis to axillary lymph nodes fixed to each other or to other structures, conglomerate or adherent
	N2b: Clinically, there is only metastasis to the ipsilateral internal mammary lymph nodes.
N3	Metastasis to infraclavicular lymph nodes or clinically detected metastases to ipsilateral internal mammary lymph nodes or metastases to axillary or supraclavicular nodules with clinical metastasis to axillary lymph nodes.
	N3a: Metastasis to ipsilateral infraclavicular lymph nodes
	N3b: Metastasis to ipsilateral internal mammary and axillary lymph nodes
	N3c: Metastasis to ipsilateral supraclavicular nodules
Distant Metastasis (M)	
M0	No clinical or radiological evidence of distant metastasis
cM0(i+)	There are molecular deposits or microscopic tumor cells no larger than 0.2 mm in the bloodstream, bone marrow, or non-regional lymph nodes only.
M1	There are distant metastases determined by clinical and radiological methods.

*Pectoral muscle invasion and invasion of the dermis alone cannot be defined as T4

Table-2 Clinical Anatomical Staging

Stage	TNM
Stage 0	Tis N0M0
Stage 1A	T1N0M0
Stage 1B	T0-1 NmicM0
Stage 2A	T0-1N1M0 or T2N0M0
Stage 2B	T2N1M0 or T3N0M0
Stage 3A	T0-2N2M0 or T3N1-2M0
Stage 3B	T4N0-2M0
Stage 3C	T1-4N3M0
Stage 4	T1-4N0-3M1

The fact that breast cancer has a wide biological spectrum and different molecular subtypes has enabled prognostic and predictive factors to be included in the staging system. As a result, the clinical prognostic staging system has been developed in AJCC version 8 with the addition of parameters that directly affect the treatment plan, prognosis, and recurrence. In this staging system, in addition to TNM, histological grade (HG), HER-2 receptor, estrogen receptor (ER), and progesterone receptor (PR) information obtained from the biopsy material are also used. In the pathological prognostic staging system in which the information obtained from the surgical material is used, the genetic profile of the tumor (Oncotype Dx 21-gene analysis, Mammaprint 70 gene analysis, etc.) and the levels of circulating cancer cells and destruction products (miRNA and DNA) in the blood are also included in the 8th version of AJCC. The clinical prognostic staging system is shown in Table-3.

Table-3 Clinical Prognostic Staging System

		ER+/PR+ HER2+	ER+/PR+ HER2+	ER+/PR+ HER2+	ER-/PR+ HER2+	ER-/PR- HER2+	ER+/PR+ HER2+	ER-/PR+ HER2+	ER-/PR- HER2+
TİSN0M0 G1-3		0	0	0	0	0	0	0	0
T1N0M0 T0N1miM0 T1N1miM0	G1.	E1A	E1A	E1A	E1A	E1A	E1A	E1A	E1B
	G2.	E1A	E1A	E1A	E1A	E1A	E1A	E1A	E1B
	G3.	E1A	E1A	E1A	E1A	E1A	E1A	E1B	E1B
T0N1M0 T1N1M0 T2N0M0	G1.	E1B	E1B	E2A	E2A	E2A	E2A	E2A	E2A
	G2.	E1B	E1B	E2A	E2A	E2A	E2A	E2A	E2B
	G3.	E1B	E2A	E2A	E2A	E2A	E2B	E2B	E2B
T2N1M0 T3N0M0	G1.	E1B	E2A	E2A	E2A	E2B	E2B	E2B	E2B
	G2.	E1B	E2A	E2A	E2A	E2B	E2B	E2B	E3B
	G3.	E1B	E2B	E2B	E2B	E2B	E3A	E3A	E3B

T0N2M0 T1N2M0 T2N2M0 T3N1M0 T3N2M0	G1. G2. G3.	E2A E2A E2B	E2A E2A E3A	E3A E3A E3A	E3A E3A E3A	E3A E3A E3A	E3A E3A E3B	E3A E3A E3B	E3B E3B E3C
T4N0M0 T4N1M0 T4N2M0 T1-4N3M0	G1. G2. G3.	E3A E3A E3B	E3B E3B E3B	E3B E3B E3B	E3B E3B E3B	E3B E3B E3B	E3B E3B E3C	E3B E3B E3C	E3C E3C E3C
T1-4N1-3M1		E4	E4	E4	E4	E4	E4	E4	E4

The clinical prognostic staging system helps to evaluate the long-term survival outcomes of patients. Studies have shown that patients with triple-negative, HER-2-negative, ER-PR-negative, and HG 3 have low anatomic stages, but have low survival rates, that is, anatomical stage and prognostic stage are not compatible [2]. Validation studies show that the prognostic staging system provides a more accurate prediction of disease survival [3,4].

RESOURCES

1. *AJCC (American Joint Committee on Cancer) Cancer Staging Manual; 8th edition, 3rd printing, Amin MB, Edge SB, Greene FL, et al (Eds), Springer, Chicago 2018.*

2. *Li X, Zhang Y, Meisel J, et al. Validation of the newly proposed American Joint Committee on Cancer (AJCC) breast cancer prognostic staging group and proposing a new staging system using the National Cancer Database Breast Cancer Res Treat. 2018; 17:303-313.*
3. *Weiss A, Chavez-MacGregor M, Lichtensztajn DY, et al. Validation Study of the American Joint Committee on Cancer Eighth Edition Prognostic Stage Compared With the Anatomic Stage in Breast Cancer. JAMA Oncol. 2018;4:203-209.*
4. *Giuliano AE, Connolly JL, Edge SB, et al. Breast Cancer-Major changes in the American Joint Committee on Cancer eighth edition cancer staging manual. CA Cancer J Clin. 2017; 67:290-303.*

5.2.1.1 Multidisciplinary Approach After Staging

As with other cancers, a continuous and regular multidisciplinary study is needed to be successful in the early diagnosis and treatment of breast cancer. Collaboration is required between radiologists, family physicians, doctors working in KETEMs, and surgeons during the screening and diagnosis stages. Imaging methods to be applied in both population-based, organized and opportunistic scans and their timing should be determined by joint evaluations of radiologists and clinicians. The same cooperation should be continued in the determination of biopsy necessity and modality. If there is inconsistency between radiological findings and pathological diagnoses, cooperation on further examination and re-biopsy decisions is very important. For diagnostic or therapeutic lumpectomies to be performed with marking methods, it is recommended that the surgeon be present during marking. Important issues such as the selection of the incision site and surgical margins are discussed and clarified together. Radiologists, nuclear medicine specialists, and other clinicians should decide together for the examinations to be performed to investigate distant metastases. In this way, unnecessary investigations and interventions can be prevented in patients with a low risk of distant metastasis, or suspicious lesions can be revealed in at-risk patients.

One of the good examples of this type of communication is the pathologist-clinician collaboration. The surgeon's orientation to the pathologist on the specimen facilitates correct decisions about surgical margins, the necessity of re-excision, and the completion of mastectomy. During the intra-operative evaluation, the pathologist and surgeon working together in the operating room on surgical margin determination and sentinel lymph node biopsy reduce the possibility of re-excision or re-operation. When there is a mismatch

between the obtained biological, prognostic and predictive parameters and the clinical status, some parameters can be re-examined.

The approaches to be followed should be determined in multidisciplinary tumor councils after all the pathological features of the patients are revealed by clinical and preferably core-needle biopsy. Medical oncology, radiotherapy, general surgery, radiology, and pathology disciplines must be present in these councils. These specialists should be intensely interested in breast cancer in their daily routine practice. When necessary, medical genetics, psychiatry, psycho-oncology, physical medicine and rehabilitation, molecular biology, nuclear medicine specialists, and breast care nurses can participate in the councils related to breast cancer. It should be considered important that specialty students and medical school students from these branches participate in these councils. Multidisciplinary councils are an important part of medicine and specialty training in medicine, and the results obtained here should be regularly presented to patients.

In tumor councils, surgery, neo-adjuvant or adjuvant chemotherapy, hormonal therapy, and radiotherapy are decided according to the stage of the disease and the molecular subtype of the tumor. In patients diagnosed with early-stage (Stage I and IIA) breast cancer and whose tumor/breast ratio is appropriate, treatment can be started with surgery. According to the pathological result obtained, adjuvant treatments (systemic chemotherapy, radiotherapy, endocrine therapy) are recommended in the tumor council. Initiating treatment with systemic therapy in locally advanced breast cancer (Stage IIB or III) has advantages such as measuring the tumor response to chemotherapy in vivo, destroying possible circulating tumor cells, downgrading the tumor, and providing an opportunity for breast-conserving surgery and axilla preservation. Radiotherapy is applied as a standard treatment for patients who underwent breast-conserving surgery and patients diagnosed with locally advanced breast cancer. Radiotherapy is also required in some mastectomy patients and patients with metastatic breast cancer.
Approximately 70% of patients diagnosed with breast cancer are estrogen receptor-positive, and endocrine therapy is applied to these patients after systemic therapy.

Although there are useful guides on treatment algorithms, it should not be forgotten that each patient should be evaluated within the framework of their own characteristics (personalized treatment). Although many parameters are effective in the choice of surgical

technique and adjuvant treatment decisions, it should be kept in mind that patient preference, age, comorbidity, habits, education level, socio-cultural status, and even access to the hospital are effective in these decisions. In tumor councils, all the characteristics of the patient are evaluated together and the most accurate decision is tried to be reached. On the other hand, modern medicine is an extremely dynamic process. Following the literature, documenting the centers' own data, planning clinical studies, creating algorithms, and standardizing some procedures can only be achieved with a multidisciplinary study.

It has been found that there is a 20% reduction in breast cancer-specific mortality in experienced centers where multi-disciplinary breast cancer diagnosis and treatment are performed [1-3]. It has been observed that patients treated in these centers feel more secure, cope with stress more easily, and have a higher quality of life [4]. Another study demonstrating the importance of multidisciplinary working principles was reported by the University of South Carolina [5]. In this study, it was determined that significant changes were made in terms of diagnosis, examination, and treatment in 42% of the patients discussed in tumor councils. All these facts have brought the establishment and development of breast excellence centers to the agenda. If necessary, the idea of treating breast cancer cases only in such centers is discussed.

RESOURCES

1. *Kingsmore D, Ssemwogerere A, Hole D, Gillis C. Specialization and breast cancer survival in the screening era. Br J Cancer 2003; 88:1708-12,*
2. *Kesson EM, Allardice GM, George WD, Burns HJ, Morrison DS. Effects of multidisciplinary team working on breast cancer survival: a retrospective, comparative, interventional cohort study of 13 722 women. BMJ. 2012; 344:2718-2723.*
3. *Brown ER, Bartlett J, Chalulu K, et al. Development of multi-disciplinary breast cancer care in Southern Malawi. Eur J Cancer Care. 2017;26(1).*
4. *Dionigi F, Milani R, Garcia-Etienne CA, Praticò V, Riboni G. The institution of a Multi-disciplinary Italian Breast Unit: Reflections of the first psychosocial research study results on distress and quality of life. Breast J. 2019; 25:678-681*
5. *Garcia D, Spruill LS, Irshad A, et al. The Value of a Second Opinion for Breast Cancer Patients Referred to a National Cancer Institute (NCI)-Designated Cancer Center with a Multidisciplinary Breast Tumor Board. Ann Surg Oncol. 2018; 25:2953-2957.*

5.2.3. Treatment in Breast Cancer

5.2.3.1.Surgical Treatment in Breast Cancer

Surgical Treatment in Ductal Carcinoma In Situ (DCIS)

Ductal Carcinoma In Situ (DCIS) refers to a heterogeneous group of neoplastic lesions originating from the mammary ducts and not exceeding the basement membrane layer. With the spread of breast cancer screening programs in the world, there has been an increase in the frequency of diagnosis. DCIS accounts for more than 20% of newly diagnosed breast cancers in countries where screening programs have been successfully implemented [1]. The aim of DCIS treatment is to eliminate the tumor before the disease turns into invasive cancer. Surgical treatment, radiotherapy (RT) and endocrine therapy are among the treatment options used for this purpose. The basis of treatment is surgical removal of the tumor with negative surgical margins. Breast conserving surgery (BCS) and mastectomy are methods used for this purpose. Although BCS is the method that should be preferred first, not all patients may be suitable for this intervention. BCS can be performed as a traditional lumpectomy (wide excision or partial mastectomy) or by using oncoplastic surgery (OPC) techniques. Radiotherapy (RT) is added as a standard treatment after BCS. However, the place of RT in a low-risk patient group is debated [2]. The goal of BCS is to provide complete excision of the lesion with intact surgical margins and to achieve acceptable cosmetic results. BCS cannot be performed in cases where it is not possible to obtain histologically sound surgical margins. In a joint study of the American Society of Clinical Oncology (ASCO), Society of Surgical Oncology (SSO) and American Society for Radiation Oncology (ASTRO) in 2016, a surgical margin of 2 mm was found to be sufficient for DCIS. However, resection is not recommended for all patients with a surgical margin of fewer than 2 millimeters. Factors that increase the risk of local recurrence for re-excision (such as comedonecrosis, high grade, young age, hormone receptor negativity) should be considered [3]. On the other hand, it is controversial that the concept of "no tumor cell seen in the ink-painted border" accepted for invasive tumors at the 14th StGallen International BreastCancer Conference can be accepted as an adequate surgical margin for DCIS [4]. Lesions located in the same quadrant or in close quadrants and not far

from each other (multifocal/multicentric disease) do not constitute a contraindication for

BCS. Lesions that are distant from each other and located in different quadrants are considered a relative contraindication.

Cosmetic results are directly related to the tumor/breast size ratio and the location of the lesion. Today, the frequency of OPC use is increasing for larger tumors and more difficult localizations [5]. In this way, since larger tumors can be removed more widely, it is more likely to provide a surgical margin above 2 mm. OPC provides a reduction in re-excision and re-operation rates and an increase in breast-conserving surgery [6]. It should be noted that re-excisions increase patient anxiety and treatment costs while impairing cosmetic results [7]. Mastectomy should be preferred in cases where it is not possible to provide adequate surgical margins and good cosmetic results such as diffuse microcalcifications. Simultaneous autologous or implant-based reconstruction alternatives with mastectomy should be offered to the patient.

DCIS is frequently encountered as microcalcifications on mammography. In such a case, the areas that need to be removed in order to obtain a solid surgical margin are marked with wire or other marking methods, accompanied by mammography. It is checked whether the lesion is completely removed by taking the film of the removed tissue (specimen graph) [8]. In doubtful cases, residual microcalcifications should be evaluated by mammography after surgical intervention and re-excision should be performed if necessary [9].

Although there is no theoretical risk of local recurrence in patients undergoing mastectomy, local recurrence has been observed at a rate of 1-2% in some series [10]. Overlooked invasive disease, inadequate surgical margins, or failure to remove all of the breast tissue attached to the skin are thought to be the cause of local recurrence. Choosing a mastectomy in a patient who is suitable for BCS should be considered an unnecessary and excessive treatment. Although local recurrence rates after BCS were slightly higher than mastectomy, no difference was found in long-term survival outcomes. In addition, complication rates are lower after BCS [11]. The main cause of death in DCIS is invasive breast cancer that recurs in the same breast or occurs in the opposite breast. Considering the long-term follow-up results of 108,196 patients with DCIS in the Surveillance Epidemiology and End Results (SEER) database, the 20-year breast cancer-specific mortality was found to be 3.3%. This rate is higher in patients younger than 35 years of age. While the rate of ipsilateral invasive breast cancer was found to be 4.9% in patients who had only BCS, this

rate drops to 2.5% when RT is added to BCS. There was no significant difference in breast cancer-specific survival between patients who underwent BCS with RT and those who underwent mastectomy [12].

In another study involving 140,366 patients, the 15-year breast cancer-specific mortality was equal in patients treated with mastectomy and BCS+RT (1.7%) [13]. In the light of all this information, it can be said that BCS is the most reasonable surgical treatment option with low local recurrence rate and minimal morbidity in suitable patients. However, all treatment options should be discussed and decided with the patient. The risk of developing DCIS or invasive breast cancer in the contralateral breast in patients who have been operated on for DCIS increases by 1% each year. Therefore, prophylactic mastectomy for the other breast can also be discussed with the patient [14]. However, the contribution of contralateral prophylactic mastectomies to survival has not been demonstrated [15]. Patients treated with bilateral mastectomy do not need to receive adjuvant endocrine therapy.

Theoretically, there is no need for sentinel lymph node biopsy (SLNB) in patients with pure DCIS since lesions that do not invade the basement membrane do not have a risk of axillary metastasis. However, SLNB is recommended especially for lesions diagnosed with thick needle biopsy and clinically and radiologically suspected of invasion/microinvasion. If invasion/microinvasion is detected in the final specimen in patients who have undergone BCS but not SLNB, SLNB should be performed on these patients with a second operation. In addition, SLNB should be performed in patients who are planned for mastectomy. Because after mastectomy, the lymphatic drainage pattern of the breast is permanently impaired, and then the possibility of SLNB is eliminated. In addition, it has been reported that invasion/microinvasion is more common in patients requiring mastectomy [16].

In patients with positive estrogen or progesterone receptors, adjuvant hormone therapy is recommended for at least 5 years. RT is not required in patients who have undergone mastectomy. Anamnesis, physical examination, and annual breast imaging are sufficient in the follow-up of patients after surgery. There is no need to look for tumor markers, routine laboratory tests, and other imaging methods.

RESOURCES

1. *Ernster VL, Ballard-Barbash R, Barlow, et al. Detection of ductalcarcinoma in situ in*

womenundergoingscreeningmammography. J Natl Cancer Inst. 2002; 94:1546–54.

2. *Silverstein MJ, Lagios MD. Should all patients undergoing breast conserving therapy for DCIS receive radiation therapy? No. One size does not fit all: an argument against the routine use of radiation therapy for all patients with ductal carcinoma in situ of the breast who elect breast conservation. J Surg Oncol 2007; 95:605.*
3. *Morrow M, Van Zee KJ, Solin LJ, et al. Society of Surgical Oncology-American Society for Radiation Oncology-American Society of Clinical Oncology Consensus Guideline on Margins for Breast-ConservingSurgery with Whole-Breast Irradiation in Ductal Carcinoma In Situ.Ann Surg Oncol. 2016; 23:3801-3810.*
4. *Coates AS, Winer EP, Goldhirsch A, et al. Tailoring therapies—improving the management of early breast cancer: St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2015.Ann Oncol. 2015; 26:1533-46.*
5. *Mc Culley SJ, Durani P, Macmillan RD. Therapeutic mammaplasty for centrally located breast tumors. Plast Reconstr Surg2006; 117:366–73.*
6. *Melstrom LG, Melstrom KA, Wang EC, et al. Ductal carcinoma in situ: size and resection volüme predict magrin status. Am J Clin Oncol 2010; 33:438–42.*
7. *King TA, Sakr R, Patil S, et al. Clinical management factors contribute to the decision for contralateral prophylactic mastectomy. J Clin Oncol. 2011; 29:2158–64.*
8. *White RR, Halperin TJ, Olson JA Jr, et al. Impact of core-needle breast biopsy on the surgical management of mammographic abnormalities. Ann Surg 2001; 233:769.*
9. *Grann A, Abdou JC, Dragman N, Goodman R. The value of post excision pre radiation mammography in patients with early-stage breast cancer. Am J Clin Oncol 2004; 27:285.*
10. *Hwang ES. The impact of surgery on ductal carcinoma in situ outcomes: the use of mastectomy. J Natl Cancer Inst Monogr 2010; 2010:197.*
11. *Meijnen P, Oldenburg HS, Peterse JL, et al. Clinical outcome after selective treatment of patients diagnosed with ductal carcinoma in situ of the breast. Ann Surg Oncol 2008; 15:235.*
12. *Narod SA, Iqbal J, Giannakeas V, et al. Breast Cancer Mortality After a Diagnosis of Ductal Carcinoma In Situ. JAMA Oncol 2015; 1:888.*
13. *Giannakeas V, Sopik V, Narod SA. Association of Radiotherapy With Survival in Women Treated for Ductal Carcinoma In Situ With Lumpectomy or Mastectomy. JAMA Netw Open 2018; 1: e181100.*
14. *Gao X, Fisher SG, Emami B. Risk of second primary cancer in the contralateral breast in women treated for early-stage breast cancer: a population-based study. Int J Radiat Oncol Biol Phys 2003; 56:1366-1372.*

15. *Tuttle TM, Jarosek S, Habermann EB, et al. Increasing rates of contralateral prophylactic mastectomy among patients with ductal carcinoma in situ. J Clin Oncol 2009; 27:1362.*
16. *Virnig BA, Tuttle TM, Shamliyan T, Kane RL. Ductal carcinoma in situ of the breast: a systematic review of incidence, treatment, and outcomes. J Natl Cancer Inst 2010; 102:170.*

Surgical Treatment in Early Stage Breast Cancer

Breast cancer is the most common cancer and the cause of death in women (1). The vast majority of women with breast cancer are patients who can undergo surgery. Multidisciplinary teamwork including surgical oncology, radiation oncology, and medical oncology is required for the diagnosis and treatment management of breast cancer (2). In this multi-disciplinary approach, the preference of the patient should also be taken into account. Most patients with newly diagnosed breast cancer do not have distant metastases. The TNM classification is used in the treatment of breast cancer. Non-metastatic breast cancer is grouped into two main categories. The first of these is early-stage breast cancer, which includes patients with stage I, IIA, or T2N1, a substage of stage IIB. The other main category is locally advanced breast cancer, and Stage IIB (T3N0), and IIIA-IIIB-IIIC patients are included (3).

For patients with early-stage breast cancer, detailed history and physical examination, breast imaging (mammography, ultrasound, MRI), chest X-ray, liver and kidney function tests, and evaluation of blood calcium levels are usually sufficient. Breast MRI is not routinely used in early-stage breast cancer. MR evaluation may be required in tumors with lobular histology, in patients with suspected inherited breast cancer, and in suspected multicentric tumors. More detailed metastatic scanning (Thorax-Abdomen CT, bone scintigraphy, PET CT) may be required in cases with aggressive biology and clinically suspected metastasis. Surgical treatment is generally the priority in early-stage breast cancer. Neoadjuvant therapy may be prioritized in triple-negative/HER-2 positive, axilla positive cases. Surgery plays an important role in early-stage breast cancer, and the frequency of breast-conserving surgery has been increasing in recent years [4]. However, the surgical intervention to be performed should be discussed in the weekly tumor council and the final decision should be left to the patient. The sentinel lymph node method, which was first initiated by Norton with a radioisotope and continued with Guiliano in 1994 with blue dye,

still maintains its place as a standard approach in staging the axilla [5]. In patients with clinically negative axilla, sentinel lymph node biopsy using blue dye or radioisotope, sometimes both (dual method), will protect patients with negative snetinel lymph node from axillary dissection and its complications. Level 1-2 lymph node dissection is sufficient in patients who need axillary dissection [6]. Given the potential morbidity associated with axillary dissection, a less invasive method of axillary assessment appears to be the gold standard [7]. In conclusion, staging of the axilla is still an important prognostic factor for breast cancer, and sentinel lymph node biopsy and axillary dissection play an important role in prognosis and treatment. In addition to these local treatments, some patients are also given systemic treatment. The factors that play a role in the decision for adjuvant systemic therapy are the genetic profile of the tumor, its size, histological grade, the presence and number of positive lymph nodes, estrogen-progesterone receptor positivity, Her2 receptor status, and Ki67 ratio [8].

Breast Conserving Surgery (MKC)

Breast-conserving surgery (BCS) consists of the removal of the tumor with negative surgical margins (lumpectomy) and radiotherapy to the same breast. For invasive tumors in BCS, it is sufficient to have a negative surgical margin (the dye does not touch the tumor in the removed and stained specimen), while care should be taken to preserve the 2 mm margin in in situ tumors. In cases where breast shielding is applied, the breast bed should be marked with a total of 5 clips (upper, lower, inner, outer, and back) to provide additional radiation (boost) to the tumor cavity during radiotherapy to be planned later. The aim of breast-conserving surgery is to offer a cosmetically acceptable approach with a low recurrence rate and equal survival with mastectomy. It ensures the elimination of the disease without compromising oncological principles. Studies have shown similar oncological results with mastectomy [6].

In some cases, breast-conserving surgery is not appropriate;

BCS contraindications:

1- Multicentric disease (tumors in distant quadrants) 2-

Inappropriate tumor/breast ratio

3- Commonly suspected microcalcifications

4- First trimester of pregnancy

5- History of previous chest wall RT

6- Positive surgical margin despite re-excisions

7- Collagen connective tissue diseases (Especially SLE,

Cleroderma) 8- Patients who had BCS before (9)

Mastectomy

Mastectomy should be performed in patients who are not suitable for breast-conserving surgery. In cases where BCS cannot be performed due to the large tumor size, neo-adjuvant chemotherapy can reduce the lesion and protect the breast. Mastectomy should also be performed if patients do not want breast-conserving surgery or cannot receive radiotherapy [10].

Radiotherapy

Radiotherapy is a treatment method used to prevent locoregional recurrence in breast cancer, and studies show that it also increases survival. Irradiation of the breast in patients undergoing breast-conserving surgery (BCS) reduces local recurrence and provides a life expectancy similar to mastectomy.

Some patients with locally advanced breast cancer also require radiotherapy after mastectomy. These patients are mostly those with >4 positive lymph nodes, lymphovascular invasion, ≥5 cm tumor, inflammatory breast cancer, skin, and thoracic wall involvement. Giving radiation to patients with 1-3 lymph node involvement in the axilla is controversial. In the study of Raina et al., it was shown that there was no 10-year survival difference in patients who underwent mastectomy, with and without metastasis of 1-3 lymph nodes [11]. The type and timing of breast reconstruction, especially in patients who require RT after mastectomy, are gaining importance. Radiotherapy has been shown to reduce local recurrence in patients with early-stage breast cancer who underwent mastectomy but whose axilla was positive [7].

Evaluation of the Axilla

The risk of metastasis to the axilla is related to tumor size, localization, histological grade, presence of lymphovascular invasion, and molecular subtype of the tumor. Fine-

needle aspiration biopsy (FNAB) of this lymph node in patients with suspected lymph node metastasis in the axilla at the time of diagnosis plays an important role in determining the approach to treatment. Today, in patients with positive FNAB results, chemotherapy (neo-adjuvant chemotherapy) is started first, according to the molecular structure of the tumor. If the biopsy result is negative and the tumor size does not prevent breast preservation, sentinel lymph node biopsy (SLNB) should be performed on the patient and a decision should be made for axillary dissection based on the result. SLNB should be performed in patients with clinically and radiologically negative axilla.

SNLB is done in two ways. These are the blue dye (busulphan blue, isosulphan blue, or methylene blue) and the radioisotope method. These methods can be applied separately as well as together (combined, dual method). The dual method increases the SLN detection rate above 90% and reduces the false-negative rate below 5%.

In terms of the size of metastases detected in the lymph node in SNLB positive patients, they are divided into 3 groups:

1- Isolated tumor cell: The diameter of the metastasis in the lymph node is less than 0.2 mm.

2- Micrometastasis: The diameter of the metastasis in the lymph node is between 0.2 mm and 2 mm. 3- Macrometastasis: The diameter of the metastasis in the lymph node is more than 2 mm.

In the IBCSG 23-01 (International Breast Cancer Study Group) study conducted in 2001, patients with T1-2 tumors and micrometastases were randomized into two groups, and axillary lymph node dissection (ALND) was performed in one group and not in the other group [12]. In this study, 90% of the patients underwent BCS and received RT. Tumor diameter was smaller than 2 cm in 68% of the patients included in the study, micrometastases were present in the ER (+) in 90% and SLN in 2/3. When the groups were compared, it was shown that there was no difference between disease-free and overall survival. In addition, local recurrence rates were found to be 0.2% in the ALND group and 1.1% without treatment. Based on the results of this study, it was concluded that ALND is not needed in patients with micrometastases in the SLN [12].

In the AMAROS (EORTC 10981-22023) study, patients with cT1-2N0M0 tumor and SLNB (+) were randomized into two groups who underwent axillary dissection or axillary

RT, and it was found that there was no difference between the groups in terms of 5-year loco-regional recurrence, disease-free survival, and overall survival and the frequency of lymphedema was found to be lower in the group receiving RT [13].

In the ACOSOG Z0011 study, patients with cT1-2 N0M0 underwent BCS and SLNB, and patients with 1-2 positive lymph nodes were randomized into 2 groups [14]. While ALND was done to one group, it was not done to the other group. When these two groups were compared, it was seen that there was no difference between them in terms of overall and disease-free survival. This study showed that ALND is not required in patients with cT1-2, N0M0 who underwent BCS and who had one or two lymph nodes positive in the SLNB.

Adjuvant Systemic Therapy

Adjuvant systemic therapy in breast cancer is named in three different ways: endocrine therapy, targeted therapy, or systemic chemotherapy. Drugs such as tamoxifen and aromatase inhibitor used in endocrine therapy, trastuzumab, and pertuzumab applied in HER-2 positive patients are called targeted therapy.

The patient's age, comorbidities, the genetic profile of the tumor, prognostic and predictive factors (hormone receptor positivity, HER-2 receptor, tumor diameter, histological grade, lymphovascular invasion, lymph node involvement, tumor growth rate, etc.) play a role in the adjuvant systemic treatment decision. Systemic chemotherapy is added to the treatment in patients with HER-2 positive and triple-negative molecular subtype greater than 5 mm. After systemic therapy, patients with positive hormone receptors are given tamoxifen if they are premenopausal, and aromatase inhibitors or tamoxifen if they are postmenopausal for at least 5 years. Endocrine therapy can also be initiated during radiotherapy [15].

RESOURCES

1.Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. CA: A Cancer Journal for Clinicians. 2020;70(1):7-30.

2.Kesson EM, Allardice GM, George WD et al. Effects of multidisciplinary team working on breast cancer survival: retrospective, comparative, interventional cohort study of 13 722 women. bmj. 2012;344:e2718.

3. Weiss A, Chavez-MacGregor M, Lichtensztajn DY, et al. Validation Study of the American

Joint Committee on Cancer Eighth Edition Prognostic Stage Compared With the Anatomic Stage in Breast Cancer. JAMA Oncol. 2018;4:203–209.

4.Kummerow KL, Du L, Penson DF et al. Nationwide trends in mastectomy for early-stage breast cancer. JAMA Surgery. 2015;150(1):9-16.

5.Krag DN, Weaver DL, Alex JC et al. Surgical resection and radiolocalization of the sentinel lymph node in breast cancer using a gamma probe. Surgical Oncology. 1993;2(6):335-40.

6.Shenkier T, Weir L, Levine M et al. Clinical practice guidelines for the care and treatment of breast cancer: 15. Treatment for women with stage III or locally advanced breast cancer. CMAJ. 2004;170(6):983-94.

7.McGale P, Taylor C, Correa C et al. Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials. Elsevier; 2014.

8.Von Minckwitz G, Schneeweiss A, Loibl S, Salat C et al. Neoadjuvant carboplatin in patients with triple-negative and HER2-positive early breast cancer (GeparSixto; GBG 66): a randomised phase 2 trial. The lancet oncology. 2014;15(7):747-56.

9.Haffty BG. Controversial indications for breast conserving therapy and radiation. Breast Surgical Techniques and Interdisciplinary Management: Springer; 2010. p. 917-26.

10.Feigelson HS, James TA, Single RM et al. Factors associated with the frequency of initial total mastectomy: results of a multi-institutional study. Journal of the American College of Surgeons. 2013;216(5):966-75.

11.Raina V, Bhutani M, Bedi R et al. Clinical features and prognostic factors of early breast cancer at a major cancer center in North India. Indian journal of cancer. 2005;42(1):40.

12.Galimberti V, Cole BF, Zurrida S et al. Axillary dissection versus no axillary dissection in patients with sentinel-node micrometastases (IBCSG 23–01): a phase 3 randomised controlled trial. The lancet oncology. 2013;14(4):297-305.

13.Donker M, van Tienhoven G, Straver ME et al. Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer (EORTC 10981-22023 AMAROS): a randomised, multicentre, open-label, phase 3 non-inferiority trial. The Lancet Oncology. 2014;15(12):1303-10.

14. Giuliano AE, Hunt K, Ballman KV et al. Ten-year survival results of ACOSOG Z0011: A randomized trial of axillary node dissection in women with clinical T1-2 N0 M0 breast cancer who have a positive sentinel node (Alliance). American Society of Clinical Oncology; 2016.

15. Dellapasqua S, Colleoni M, Gelber RD, Goldhirsch A. Adjuvant endocrine therapy for premenopausal women with early breast cancer. Journal of clinical oncology. 2005;23(8):1736-50.

4. Surgical Treatment in Locally Advanced Breast Cancer

Today, cT3N0 (Stage IIB) and Stage III breast cancer are considered locally advanced breast cancer (LABC). Both local-regional and systemic recurrence risks are higher in LIBC [1-3].

Diagnosis in locally advanced breast cancer (LABC)

In patients with clinical and radiological diagnosis of LABC, a definitive diagnosis should be made by performing a core needle biopsy from the mass in the breast, and features such as tumor receptors, histological type, histological grade, Ki67 must be obtained. If there is a suspicious lymph node in the axilla, metastasis should be confirmed by ultrasonography-guided FNAB. In patients who will be given neo-adjuvant chemotherapy, the tumor in the breast and lymph node in the axilla disappear in patients who have a total response to chemotherapy. Therefore, tumor in the breast and metastatic lymph nodes in the axilla should be marked during biopsies. In this way, the area where the tumor is located is tried to be removed before the treatment. In some patients, the marker placed on the breast is displaced after chemotherapy. In these patients, the radiologist can make a new marking according to the localization of the tumor in the mammography performed before the treatment. The false-negative rate is high in SLNBs performed after neo-adjuvant chemotherapy [4]. Therefore, marking a positive lymph node in the axilla before chemotherapy and removal of the same lymph node during SLNB after chemotherapy reduces the false-negative rate [5]. Avoiding overtreatment should be the most important goal when planning personalized treatment. Molecular subtype analysis of the tumor should be performed according to the core needle biopsy result, and surgical treatment should be given priority in patients whose total response rate to systemic therapy does not exceed 10-15% [6-7].

Since there is a risk of distant metastasis in patients diagnosed with LABC, systemic dissemination should be investigated before starting treatment. For this purpose, PET-CT or thorax-abdominal CT, bone scintigraphy and brain imaging are used.

When planning the treatment of locally advanced breast cancer matters need to be considered such as:

- Time of surgical treatment
- Ideal neo-adjuvant chemotherapy regimen
- The place of breast conserving therapy
- Approach to the axilla before and after neo-adjuvant chemotherapy, sentinel lymph node biopsy (SLNB)
- The points such as breast reconstruction need to be taken into consideration.

Although neo-adjuvant chemotherapy does not provide a survival advantage, it is preferred since it enables early treatment in the disease thought to be systemic, reduces the stage of the tumor (*down staging*), provides operability and BKC, and gives the chance to evaluate the response to chemotherapy in-vivo. In addition, total response rates to neo-adjuvant chemotherapy with new chemotherapeutic drugs and ***targeted therapy*** reach 40% in triple-negative cancer and 60% in HER-2 positive cancer.

In patients who respond very well to neo-adjuvant chemotherapy, the chance of breast and axilla preservation increases. In order to evaluate this response, radiological examinations (mammography/ultrasonography/MR) performed before treatment should also be repeated after treatment. There is usually no need to re-examine for the systemic spread in patients who initially did not have a systemic spread and had a good response to treatment. BCS indications in patients diagnosed with LABC are similar to those in early-stage breast cancer.

If the axilla is clinically negative (cT3N0M0) in patients with LABC, SLNB is not recommended before chemotherapy. However, SLNB can be performed after chemotherapy and if negative, axillary dissection can be avoided. If the axilla is positive at diagnosis and negative after chemotherapy, SLNB can be performed. The application of two methods (dual method) during this procedure increases the rate of finding the lymph node. Removal of at

least 3 lymph nodes (if any marked lymph node is present) during SLNB reduces the false-negative rate. Avoidance of axillary dissection in patients with negative SLN after neo-adjuvant chemotherapy is not a standardized treatment today. These patients receive radiotherapy after surgery and endocrine therapy if they are estrogen receptor-positive. Radiotherapy is almost the standard treatment after surgery in the treatment of locally advanced breast cancer. Only pT3N0M0 cases can be exempted from radiotherapy by being evaluated in a multidisciplinary tumor council. Alternative chemotherapy options are applied in patients who do not respond adequately to chemotherapy [8-9].

To summarize, LABC is a risky group in terms of both local recurrence and distant metastasis. Although neoadjuvant chemotherapy does not usually provide a life advantage, it can be used in selected patients, especially in triple-negative and HER-2 positive cases, as it increases the chance of breast conserving surgery and the chance of SLNB. It is important to evaluate patients in multidisciplinary tumor councils for LABC treatment planning [1-10].

RESOURCES

1. *Rosenbluth JM, Overmoyer BA. Inflammatory Breast Cancer: a Separate Entity. Curr Oncol Rep. 2019 Aug 15;21(10):86. doi: 10.1007/s11912-019-0842-y.*
2. *Fowler AM, Mankoff DA, Joe BN. Imaging Neoadjuvant Therapy Response in Breast Cancer. Radiology. 2017 Nov;285(2):358-375*
3. *Wolmark N, Wang J, Mamounas J et al.. Preoperative Chemotherapy in Patients With Operable Breast Cancer: Nine-Year Results From National Surgical Adjuvant Breast and Bowel Project B-18. JNCI Monographs, Volume 2001, Issue 30, December 2001, Pages 96–102*
4. *Ozmen V, Unal ES, Muslumanoglu ME, et al. Axillary sentinel node biopsy after neoadjuvant chemotherapy. Eur J Surg Oncol. 2010 Jan;36(1):23-9. doi: 10.1016/j.ejso.2009.10.015. PMID: 19931375*
5. *Cabıoğlu N, Karanlık H, Ozmen V et al. Improved False-Negative Rates with Intraoperative Identification of Clipped Nodes in Patients Undergoing Sentinel Lymph Node Biopsy After Neoadjuvant Chemotherapy. Ann Surg Oncol. 2018 Oct;25(10):3030-3036. doi: 10.1245/s10434-018-6575-6. Epub 2018 Jul 5.*
6. *Bear HD, Anderson S, Smith RE et al: Sequential preoperative or postoperative docetaxel added to preoperative doxorubicin plus cyclophosphamide for operable breast cancer: NSABP B-27. J Clin Oncol 2006; 2: pp. 2019-2027*

7. *Classe JM, Bordes V, Campion L, et al. Sentinel Lymph Node Biopsy After Neoadjuvant Chemotherapy for Advanced Breast Cancer: Results of Ganglion Sentinelle et Chimiothe´rapie Neoadjuvante, a French Prospective Multicentric Study. J Clin Oncol 2009; 27(5):726-32*

8. *Classe JM, Bordes V, Campion L et al. Sentinel Lymph Node Biopsy After Neoadjuvant Chemotherapy for Advanced Breast Cancer: Results of Ganglion Sentinelle Et Chimiotherapie Neoadjuvante, a French Prospective Multicentric Study. J Clin Oncol 2008; 27:726-732.*

9. *Jian-Fei Fu JF, Hai-Long Chen HL, Yang J, et al. Feasibility and Accuracy of Sentinel Lymph Node Biopsy in Clinically Node-Positive Breast Cancer after Neoadjuvant Chemotherapy: A Meta-Analysis. PLOS ONE September 2014; 9 | e105316 September 2014 | Volume 9 | Issue 9 | e105316*

10. *Cox C , Holloway CM , Shaheta A et al. What is the burden of axillary disease after neoadjuvant therapy in women with locally advanced breast cancer ? Curr Oncol 2013;, 20 (2), 111-7 Apr 2013*

Local-regional Surgical Treatment in Metastatic Breast Cancer

Owing to modern treatments, the 5- and 10-year survival rates of patients diagnosed with breast cancer are around 90% and 84% [1]. Although it is a tumor with a better biological behavior compared to other organ cancers, the 5-year survival rate falls below 30% in case of distant metastasis [2]. It is predicted that 20-30% of patients diagnosed with early-stage breast cancer may develop distant metastases. The rate of metastatic disease (de-novo metastasis) at diagnosis in the USA is 6-10%, and this rate is higher in low-middle-income countries [3]. More than 20% of the metastatic disease involves a limited number of organs or systems, this is called oligometastatic disease. The oligometastatic disease is believed to be caused by cells with a lower proliferative index and constitutes a separate category in breast cancer. Currently, breast cancer is believed to have a broad biological spectrum between local and systemic disease, and metastatic disease is the last part of this spectrum [4]. The goals in metastatic disease are to increase the patient's quality of life and prolong life [5]. The main goals of the local-regional surgical treatment of the primary tumor are to eliminate the source that may cause a new metastasis, to repair the immune system (the primary tumor produces immunosuppressive substances), to increase the effectiveness of systemic treatment by reducing the tumor burden, and to prevent the stem cells in the bone marrow from migrating to the primary tumor and inducing metastasis. can be listed as [6].

Despite all these, reduction of anti-angiogenic factors secreted from the primary tumor, immunosuppression caused by surgical intervention and anesthesia have also been suggested as factors that may reduce the success of treatment [7].

The efficacy of primary tumor surgery in metastatic disease was initially investigated in retrospective studies with a limited number of patients [8-13]. In many studies, it has been revealed that there is a survival advantage in patients undergoing surgical intervention. Obtaining a tumor-free surgical margin, presence of oligometastatic disease, and being performed on patients with bone metastases rather than visceral organ metastases have emerged as factors that positively affect survival [8-13]. In the study of Fields et al., patients with only bone metastases had longer survival in both the surgical and systemic treatment options [14]. Harris et al. presented a meta-analysis of studies comparing patients who received chemotherapy alone and those who continued treatment with chemotherapy after surgery [15]. In this evaluation, which included a total of 28693 patients, 3-year survival was found to be 40% in the surgery option and 22% in the chemotherapy option ($p<0.001$, 95%CI:2.08-2.6). In subgroup analyzes, surgery was found to be more successful, especially in patients with small primary tumors, medical problems, and less metastatic burden. It is seen that 63% of the patients in the surgical intervention group have metastases in only one localization, and patients with only bone metastases are more common [15].

Petrelli et al.'s meta-analysis included 15 studies comparing patients who underwent surgery after chemotherapy and those who received chemotherapy alone [16]. While a survival advantage was seen in the surgical arm (HR: 0.69 (95% CI: 0.63-0.77)), young, triple-negative, oligometastatic patients with bone metastases and intact surgical margins were found to be the group that benefited most from surgical treatment [16]. Although the surgical intervention applied to the breast and axilla is controversial in the studies, there is a consensus about the negative surgical margins. It is stated that total mastectomy is not superior to breast-conserving surgery, axillary intervention is required, and axillary dissection or sentinel lymph node biopsy can be performed [17].

The facts such as patient recruitment criteria, differences in the rates of patients who underwent surgical intervention, the inclusion of patients who were later found to be metastatic, inability to show a survival advantage in patients who could not achieve negative surgical margins, and patients in the surgical option consisted of younger, better-performing patients with less tumor burden and visceral metastasis all cause objection to retrospective

studies. Randomized controlled studies were planned to answer the emerging question marks, and the first resulting study was published by Badwe et al. from India [18]. In this study, patients were randomized to surgery and observation arm after 6 cycles of anthracycline-based systemic therapy. Mean survival times were found to be 18.8 months in the surgical branch and 20.5 months in the observation branch. The authors reported that local/regional treatment did not contribute to survival in patients who responded to chemotherapy, regardless of the site and number of metastases [18]. In this study, targeted therapy was not applied in the surgical branch and in any of the HER-2 (+) patients. Palliative surgery was performed in 10% of the patients in the systemic treatment branch, and local/regional disease-free survival was found to be longer in the surgical branch. The POSYTIVE trial planned by the Austrian Breast and Colorectal Cancer Study Group was closed because of a statistically insignificant survival difference in early outcomes favoring systemic therapy [19]. It should be noted that this study included only 90 patients and that survival differences in favor of local/regional surgical treatment were observed after 2-3 years.

One of the most important studies that shed light on the literature on the surgical treatment of primary tumor in metastatic disease was carried out in our country [20]. In the study named MF07-01, patients with Novo Stage IV breast cancer were randomized to the systemic treatment branches with surgery + systemic treatment. In this study, it was observed that primary surgical treatment provided a survival advantage in the group with solitary bone metastases and only in cases with bone metastases [20]. When the long-term follow-up results were examined, 41.6% of the patients in the surgical section were alive at the end of the 5th year, while 24.4% of the patients in the systemic treatment section were alive ($p=0.005$). The rates of progression or recurrence of local/regional disease were 1% in the surgery and 11% in the systemic treatment ($p= 0.001$). While there was no difference in early period (first 30 days) mortality between the groups, it was observed that surgical treatment did not delay the initiation of systemic treatment. Although there are criticisms that the survival difference in this study is due to anti-HER-2 treatment, it was found that there was a survival difference between HER-2 negative patients.

There are two ongoing randomized controlled clinical studies on this subject. In the Japanese (PRIM–BC study) and US/Canada (ECOG EA 2108) studies, patients were randomized to surgery and systemic treatment after systemic chemotherapy. The TBCRC

013 study is another study in which treatment was initiated with induction therapy and the results of which are awaited [21].

Studies conducted on metastatic disease and trying to show the effectiveness of local/regional surgical intervention also show that breast cancer is a heterogeneous and complex disease. It can be thought that patients with extensive visceral organ metastasis and in the triple-negative subgroup do not have a high chance of benefiting from primary local/regional surgical treatment. It is a logical approach to start the treatment with systemic therapy in these patients. However, it is necessary to accept the existence of molecular subtypes that will benefit from primary local/regional surgical treatment. In these patients, starting treatment with surgical treatment may improve survival.

RESOURCES

1. *De Santis CE, Ma J, Gaudet MM, et al. Breast cancer statistics, 2019. CA Cancer J Clin: 2019.*
2. *Noone AMHN, Krapcho M, Miller D, et al. editors. SEER Cancer statistics review, 1975–2015: National Cancer Institute; 2018.*
3. *Howlader NNA, Krapcho M. SEER Fast Stats, 1975-2014. Stage Distrib. 2018: 2005–14.*
4. *Hellman S. Natural history of small breast cancers. J Clin Oncol. 1994; 12:2229-34.*
5. *Andre F, Slimane K, Bachelot T, et al. Breast cancer with synchronous metastases: trends in survival during a 14-year period. J Clin Oncol 2004; 22:3302–3308.*
6. *Pagani O, Senkus E, Wood W, et al. International guidelines for management of metastatic breast cancer: can metastatic breast cancer be cured? J Natl Cancer Inst. 2010; 102:456-63.*
7. *Retsky M, Bonadonna G, Demicheli R, et al. Hypothesis: Induced angiogenesis after surgery in premenopausal node-positive breast cancer patients is a major underlying reason why adjuvant chemotherapy works particularly well for those patients. Breast Cancer Res 2004; 6: 372-4.*
8. *Gnerlich J, Jeffe DB, Deshpande AD, et al. Surgical removal of the primary tumor increases overall survival in patients with metastatic breast cancer: analysis of the 1988-2003 SEER data. Ann Surg Oncol. 2007; 14:2187-94.*
9. *Babiera GV, Rao R, Feng L, et al. Effect of primary tumor extirpation in breast cancer patients who present with stage IV disease and an intact primary tumor. Ann Surg Oncol. 2006; 13:776-82.*
10. *Pérez-Fidalgo JA, Pimentel P, Caballero A,et al Removal of primary tumor improves*

survival in metastatic breast cancer. Does timing of surgery influence outcomes? Breast. 2011; 20:548-54.

11. *Leung AM, Vu HN, Nguyen KA, et al. Effects of surgical excision on survival of patients with stage IV breast cancer. J Surg Res 2010; 161:83–88.*
12. *Pathy NB, Verkooijen HM, Taib NA, et al. Impact of breast surgery on survival in women presenting with metastatic breast cancer. Br J Surg 2011; 98:1566–1572.*
13. *Bafford AC, Burstein HJ, Barkley CR, et al. Breast surgery in stage IV breast cancer: impact of staging and patient selection on overall survival. Breast Cancer Res Treat 2009; 115:7–12.*
14. *Fields RC, Jeffe DB, Trinkaus K, et al. Surgical resection of the primary tumor is associated with increased long-term survival in patients with stage IV breast cancer after controlling for site of metastasis. Ann Surg Oncol 2007; 14: 3345-3351.*
15. *Harris E, Mitchel B, Kell MR. Meta-analysis to determine if surgical resection of the primary tumour in the setting of stage IV breast cancer impacts on survival. Ann Surg Oncol 2013; 20: 2828-2834.*
16. *Petrelli F, Barni S. Surgery of primary tumors in stage IV breast cancer: an updated meta-analysis of published studies with meta-regression. Med Oncol. 2012; 29:3282-90.*
17. *Rapiti E, Verkooijen HM, Vlastos G, et al. Complete excision of primary breast tumor improves survival of patients with metastatic breast cancer at diagnosis. J Clin Oncol 2006: 24; 2743-2749.*
18. *Badwe RA, Parmar V, Hawaldar R, et al. Surgical removal of primary tumor and axillary lymph nodes in women with metastatic breast cancer at first presentation: a randomized controlled trial. Cancer Res 2013;73: 24-29.*
19. *Fitzal F, Bjelic-Radisic V, Knauer M, et al. Impact of Breast Surgery in Primary Metastasized Breast Cancer: Outcomes of the Prospective Randomized Phase III ABCSG-28 POSYTIVE Trial. Ann Surg. 2018 Apr 24. doi: 10.1097/SLA.0000000000002771. [Epub ahead of print]*
20. *Soran A, Ozmen V, Ozbas S, et al. Randomized Trial Comparing Resection of PrimaryTumor with No Surgery in Stage IV BreastCancer at Presentation: Protocol MF07-01. Ann Surg Oncol. 2018; 25:3141-3149.*
21. *King TA, Lyman J, Gonen M, et al. A prospective analysis of surgery and survival in stage IV breast cancer (TBCRC 013). 2016 ASCO Annual Meeting. Abstract 1006. Presented at Chicago Illinois, 4 June 2016.*

5.2.3.2. Systemic Treatment in Breast Cancer

Systemic treatments applied in breast cancer are chemotherapy, endocrine therapy and

targeted biological therapies. The aim of systemic treatment is to reduce the local, regional, and/or systemic recurrence of the tumor by taking into account the clinico-pathological characteristics of the patient, to prolong the life span of the patients, to prevent the progression of the disease in metastatic patients, and increase the life span and quality.

Chemotherapy has no place in the systemic treatment of ductal carcinoma in situ (DCIS). Following surgical treatment, endocrine therapy is given for 5 years in estrogen receptor (ER) positive patients. For this purpose, tamoxifen in pre-menopausal patients, tamoxifen or aromatase inhibitors (anastrozole, exemestane) in post-menopausal patients are recommended [1-3]. Although the HER-2 receptor positivity rate is higher than in invasive breast cancer, there is no data to support the use of HER-2 receptor antagonists in DCIS [4].

Systemic Treatment in Early Stage (Stage I, IIA) Breast Cancer

Hormone receptor (ER, PR) positive, HER2 negative Breast Cancer

Adjuvant endocrine therapy is sufficient for tumors with a tumor diameter of less than 5 mm (T1a). In patients with no lymph node involvement and a tumor >5mm, the risk of systemic metastasis within 10 years [such as the Oncotype-Dx Recurrence Score (RS)] is calculated according to the genetic characteristics of the tumor [5]. In cases where these tests cannot be performed, the treatment decision is made in the evaluation made in the multidisciplinary tumor council according to the prognostic and predictive characteristics of the patient and the tumor. Systemic therapy, including adjuvant chemotherapy, is recommended for patients with pathological lymph node involvement, regardless of tumor size. However, in a selected group of patients with pN1, a treatment decision can be made according to the Oncotype Dx-21 gene recurrence score (RS). In pre-menopausal and <40 years old patients, simultaneous medical ovarian ablation (GnRh analog) can be applied with chemotherapy. After the chemotherapy is completed, tamoxifen ± GnRh analog is added to the treatment in pre-menopausal patients, aromatase enzyme inhibitor alone in post-menopausal patients, or aromatase enzyme inhibitor after tamoxifen.

Endocrine Treatment

The most important factor when planning endocrine therapy in patients with hormone receptor positive breast cancer is the patient's menopausal status. Endocrine therapy is applied after chemotherapy in patients who are planned for adjuvant chemotherapy, but it

can be applied together with radiotherapy in patients who are scheduled for radiotherapy.

Tamoxifen is a selective estrogen receptor modulator (SERM) and can be used in pre-menopausal and post-menopausal patients. The duration of use of tamoxifen may be 5 or 10 years in pre-menopausal patients, depending on the risk of recurrence [6-8]. Depending on the use of tamoxifen, hot flashes, vaginal discharge, sexual dysfunction, menstrual irregularity may occur, and the risk of deep vein thrombosis, pulmonary embolism, weight gain, glaucoma, and endometrial cancer (3-4/10,000) may increase [9,10].

Aromatase inhibitors (AI) (anastrozole, letrozole, exemestane) are endocrine therapy agents used in post-menopausal patients. It can be used for 5-10 years depending on the risk of recurrence, and after 2-3 years of tamoxifen, aromatase inhibitors can be switched and the total endocrine treatment period can be arranged to be 5 or 10 years.
Arthralgia, myalgia, osteopenia/osteoporosis, and high cholesterol are possible side effects.

Systemic Chemotherapy

Today, multiple regimens containing anthracyclines and/or taxanes are preferred for systemic treatment [11]. Before anthracycline administration, echocardiography should be performed to measure cardiac function and ejection fraction [12]. It is recommended to start adjuvant chemotherapy 4-8 weeks after surgery. Delayed initiation of treatment reduces the survival rate [13]. The most commonly used regimens are doxorubicin/cyclophosphamide (AC), docetaxel/cyclophosphamide (TC), taxane after AC (docetaxel or paclitaxel), less frequently cyclophosphamide/methotrexate/5-fluorouracil (CMF).

Systemic Treatment of HER-2 positive Breast Cancer

An increase in HER-2 receptor expression is observed in 15-20% of patients diagnosed with breast cancer [14]. Trastuzumab is a monoclonal antibody that acts by binding to the extracellular component of the HER-2 receptor, and its most important side effect is cardiotoxicity. The functions of the heart (ejection fraction) are monitored every three months by basal echocardiography.

Adjuvant trastuzumab and chemotherapy are recommended in all patients with HER-2 positive breast cancer with lymph node positive or tumor size >1 cm. In patients with negative lymph node and/or tumor size ≤1 cm, treatment is decided by evaluating other risk factors together. Trastuzumab can be given concomitantly with taxane, endocrine therapy,

and radiotherapy, but should not be given with an anthracycline.

Hormone Receptor (HR) negative, HER-2 negative Breast Cancer (triple or triple negative breast cancer)

Adjuvant chemotherapy is the standard treatment for patients with this molecular subtype. Adjuvant systemic therapy is also not recommended for patients with a tumor diameter of <0.5 cm and negative axilla [15]. It is stated that the tumor diameter is <0.5 cm, and if there is micrometastasis in the axilla (pN1mic), chemotherapy can be considered (15).

Preoperative Systemic (Neo-adjuvant) Treatment

The fact that the totale response to chemotherapy is over 50% owing to new and effective chemotherapeutic drugs, and that targeted therapies can be used effectively in approximately 90% of patients, except for triple negative breast cancer, has brought the use of neoadjuvant chemotherapy in early-stage breast cancer to the agenda.

Objectives of neo-adjuvant systemic therapy;

1. Evaluating the effect of 'in vivo' treatment on the tumor, 2. Destroying

Circulating Tumor Cells, 2. Down-staging the disease,

3. To ensure operability by reducing the primary tumor and its metastases in in-operable cases, 4. To enable breast-conserving surgery by shrinking the tumor in patients with a large tumor/breast ratio,

5.It can be listed as making the axilla negative in patients with positive axilla at the time of diagnosis and avoiding axillary dissection [16].

Neo-adjuvant systemic therapy is recommended as a standard treatment for locally advanced breast cancer (LABC, Stage IIB and III).

Since the rate of total response to neo-adjuvant systemic therapy is low in patients with hormone receptor (HR) positive and luminal A molecular subtype (10-15%), treatment can be started with surgery after diagnosis. Trastuzumab (±pertuzumab) is given together with neoadjuvant chemotherapy in HER-2 receptor positive patients. If HR is strongly positive, HG and Ki67 are low (<20%), and HER-2 is negative, endocrine therapy for at least 4 months, preferably 6 months, can be considered as neo-adjuvant therapy, especially in

elderly patients and those with comorbid diseases. In other patients, trastuzumab ± pertuzumab should be added to the treatment in HER-2 positivity in addition to combinations containing anthracycline and taxane.

Systemic Treatment in Stage 4 (metastatic) Breast Cancer

In patients with systemic metastases, the location of the metastasis, the characteristics of the tumor, the performance of the patient, the associated diseases (heart failure, coronary artery disease, chronic obstructive pulmonary disease, kidney failure, etc.) and previous treatments are the factors that affect the palliative treatment decision.

In biopsies performed from metastases, approximately 20% of patients may encounter HR and/or HER-2 receptor status different from the receptors of the primary tumor. Therefore, in patients with local or systemic recurrence, biopsies from the tumor should be compared with the receptors of the primary tumor and a treatment decision should be made accordingly [7,8].

In the systemic treatment of metastatic breast cancer, chemotherapy (anthracycline, taxane, capecitabine, gemcitabine, vinorelbine, etc.) is mostly preferred as monotherapy in order to reduce toxicity. When adding anti-HER2 drugs in HER-2 positive patients, care should be taken in terms of drug interactions. Again, anthracycline should not be the first choice in patients who received anthracyclines during adjuvant chemotherapy due to the cumulative dose effect (total dose should not exceed 350-400 mg/m2 in terms of cardiotoxicity).

Endocrine therapy should be preferred in **HR positive /HER-2** receptor negative disease in the absence of rapid progression, symptomatic disease or visceral crisis due to metastasis. In HR positive patients, besides tamoxifen and aromatase inhibitors, cyclin dependent kinase 4/6 inhibitors (CDK 4/6 inhibitors), which are active on the cell cycle, are also used. Palbociclib, ribociclib, abemaciclib are CDK 4/6 inhibitors, and their use in combination with standard endocrine therapy has been shown to be effective [19-24].

Table 4. Endocrine Treatment Options in Hormone Receptor Positive Metastatic Disease

Letrozole Anastrozol e Tamoxifen Fulvestrant	Letrozole+palbociclib/ribociclib(CDK4/6 inhibitor) Fulvestrant + palbociclib/ribociclib Fulvestrant +anastrozole

In HER-2 receptor positive disease, chemotherapy is added in addition to anti-HER-2 drugs, or endocrine therapy is added in HR positive patients. Anti-HER2 drugs are trastuzumab, pertuzumab, lapatinib, and TDM1, a monoclonal antibody conjugate with a cytotoxic agent.

In **triple negative (HR and HER-2 receptor negative)** disease, chemotherapy is the most important treatment option. Studies are ongoing to add immunotherapy to chemotherapy in selected patients [25–26]. Patients with BRCA mutations usually have a triple-negative molecular structure, and PARP inhibitors have been shown to be effective in these [25–26].

Osteoclast inhibitors in patients with bone metastases

Osteoclast inhibitors are used in the treatment of bone metastases and the prevention of related complications in patients diagnosed with breast cancer [27-28]. Denosumab (RANKL inhibitor) or bisphosphonates (zoledronic acid, ibandronic acid, clodronic acid) are added to systemic treatment in these patients. The main mechanism of action of bisphosphonates is the apoptosis of osteoclasts and inhibition of their activity. In this way, it inhibits the release of calcium from the bones and prevents bone resorption. It has been shown that in patients using bisphosphonates, pathological fractures that may occur in the bones and pressure on the spinal cord are less, and less radiotherapy or surgical intervention is required for the bones. Patients should be followed in terms of mandibular necrosis and kidney failure, which are the complications of these drugs. It is recommended to avoid invasive dental treatment (implants etc.) when using bisphosphonates [27-28].

RESOURCES

1. *Wapnir IL, Dignam JJ, Fisher B, et al. Long-term outcomes of invasive ipsilateral breast tumor recurrences after lumpectomy in NSABP B-17 and B-24 randomized clinical trials for DCIS. J Natl Cancer Inst 2011; 103(6):478-488.*
2. *Forbes JF, Sestak I, Howell A, et al. Anastrozole versus tamoxifen for the prevention of locoregional and contralateral breast cancer in postmenopausal women with locally excised ductal carcinoma in situ (IBIS-II DCIS): a double-blind, randomised controlled trial. Lancet 2016; 387(10021): 866-873.*
3. *Margolese RG, Cecchini RS, Julin TB, et al. Anastrozole versus tamoxifen in postmenopausal women with ductal carcinoma in situ undergoing lumpectomy plus radiotherapy (NSABP B-35): a randomized, double-blind, phase 3 clinical trial. Lancet 2016; 387(10021): 849-856.*
4. *Kuerer HM, Buzdar AU, Mittendorf EA, et al.Biologic and immunologic effects of preoperative trastuzumab for ductal carcinoma in situ of the breast.Cancer 2011; 117(1): 39-47.*
5. *Henry NL, Somerfield MR, Abramson VG, et al. Role of Patient and Disease Factors in Adjuvant Systemic Therapy Decision Making for Early-Stage, Operable Breast Cancer: American Society of Clinical Oncology Endorsement of Cancer Care Ontario Guideline Recommendations. J Clin Oncol 2016; 34(19): 2303-2311.*
6. *Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials Lancet 2005; 365(9472): 1687-1717.*
7. *Davies C, Pan H, Godwin J, et al. Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of oestrogen receptor-positive breast cancer: ATLAS, a randomised trial.Lancet 2013; 381(9869): 805-816.*
8. *Francis PA. Adjuvant ovarian suppression in premenopausal breast cancer. N Engl J Med 2015; 372: 436–446.*
9. *Fisher B, Constantino JP, Wickerham DL, et al. Tamoxifen for the prevention of breast cancer: current status of the National Surgical Adjuvant Breast and Bowel Project P-1 study. J Natl Cancer Inst 2005; 97(22):1652-1662.*
10. *Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Davies C, Godwin J, Gray R, et al, Relevance of breast cancer hormone receptors and other factors to the efficacy of*

adjuvant tamoxifen: patient-level meta-analysis of randomized trials. Lancet 2011; 378 (9793): 771-784.

11. *Early Breast Cancer Trialists' Collaborative Group (EBCTCG), Peto R, Davies C, Godwin J, et al. Comparisons between different polychemotherapy regimens for early breast cancer: meta-analyses of long-term outcome among 100,000 women in 123 randomized trials. Lancet 2012; 379(9814): 432-444.*
12. *Jones SE, Savin MA; Holmes FA, et al. Phase III trial comparing doxorubicin plus cyclophosphamide with docetaxel plus cyclophosphamide as adjuvant therapy for operable breast cancer. J Clin Oncol 2006; 24(34): 5381-5387.*
13. *Kupstas AR, Hoskin TL, Day CN, et al. Effect of Surgery Type on Time to Adjuvant Chemotherapy and Impact of Delay on Breast Cancer Survival: A National Cancer Database Analysis..Ann Surg Oncol 2019; 26(10):3240-3249.*
14. *Noone AM, Crnin KA, Altekruse SF, et al. Cancer Incidence and Survival Trends by Subtype Using Data from the Surveillance Epidemiology and End Results Program, 1992-2013.Cancer Epidemiol Biomarkers Prev 2017; 26(4):632-641.*
15. *https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf*
16. *Park YH, Kim ST, Cho EY, et al. A risk stratification by hormonal receptors (ER, PgR) andHER-2 status in small (< or = 1 cm) invasive breast cancer: who might be possible candidates for adjuvant treatment? Breast Cancer Res Trea 2010; 119:653–661.*
17. *Pusztai L, Viale G, Kelly CM, et al. Estrogen and HER-2 receptor discordance between primary breast cancer and metastasis. Oncologist 2010; 15(11):1164-1168.*
18. *Cardoso F, Senkus E, Costa A, et al. 4th ESO-ESMO International Consensus Guidelines for Advanced Breast Cancer (ABC 4). Ann Oncol 2018; 29(8):1634-1657.*
19. *Finn RS, Martin M, Rugo HS, et al. Palbociclib and Letrozole in Advanced Breast Cancer. N Engl J Med 2016; 375(20):1925-1936.*
20. *Hortobagyi GN, Stemmer SM, Burris HA, et al. Updated results from MONALEESA-2, a phase III trial of first-line ribociclib plus letrozole versus placebo plus letrozole in hormone receptor-positive, HER2-negative advanced breast cancer.Ann Oncol 2018; 29(7): 1541-1547.*
21. *Goetz MP, Toi M, Campone M, et al. MONARCH 3: Abemaciclib As Initial Therapy for Advanced Breast Cancer. J Clin Oncol 2017; 35(32):3638-3646.*

22. *Cristofanilli M, Turner NC, Bondarenko I, et al. Fulvestrant plus palbociclib versus fulvestrant plus placebo for treatment of hormone-receptor-positive, HER2-negative metastatic breast cancer that progressed on previous endocrine therapy (PALOMA-3): final analysis of the multicentre, double-blind, phase 3 randomised controlled trial. Lancet 2016; 17(4):425-439.*

23. *Sledge GW Jr, Toi M, Neven P, et al. MONARCH 2: Abemaciclib in Combination With Fulvestrant in Women With HR+/HER2- Advanced Breast Cancer Who Had Progressed While Receiving Endocrine Therapy.J Clin Oncol 2017; 35(25):2875-2884.*

24. *Slamon DJ. Neven P, Chia S, et al. Phase III Randomized Study of Ribociclib and Fulvestrant in Hormone Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Advanced Breast Cancer: MONALEESA-3.J Clin Oncol 2018; 36(24):2465-2472.*

25. *Robson ME, Tung N, Conte P, et al. OlympiAD final overall survival and tolerability results: Olaparib versus chemotherapy treatment of physician's choice in patients with a germline BRCA mutation and HER2-negative metastatic breast cancer. Ann Oncol 2019; 30(4):558-566.*

26. *Ettl J, Quek RGW, Lee KH, et al. Quality of life with talazoparib versus physician's choice of chemotherapy in patients with advanced breast cancer and germline BRCA1/2 mutation: patient-reported outcomes from the EMBRACA phase III trial.Ann Oncol 2018; 29(9):1939-1947.*

27. *Wong MH, Stockler MR, Pavlakis N. Bisphosphonates and other bone agents for breast cancer. Cochrane Database Syst Rev 2012; 2: CD003474.*

28. *Lipton A, Theriault RL, Hortobayi GN, et al. Pamidronate prevents skeletal complications and is effective palliative treatment in women with breast carcinoma and osteolytic bone metastases: long term follow-up of two randomized, placebo-controlled trials. Cancer 2000; 88:1082-1090.*

5.2.3.3. Radiotherapy in Breast Cancer Treatment

Radiotherapy in the Treatment of Ductal Carcinoma In Situ (DCIS)

The aim of the treatment of Ductal Carcinoma in situ (DCIS) is to eliminate the risk of invasive breast cancer. While mastectomy was a standard approach in the past, breast-conserving treatment has replaced mastectomy in a very significant proportion of patients today. Breast-conserving therapy is radiotherapy of the whole breast (TMRT) after the removal of the tumor with a negative surgical margin. Today, mastectomy is recommended in cases of the multicentric disease, large tumor-small breast, extensive microcalcification

on mammography, or a situation that will prevent the patient from taking TMRT, or if recurrence occurs in the same breast after breast-conserving surgery (BC) + TMRT. If surgical margins are negative after mastectomy, there is no indication for adjuvant RT.

The aim of TMRT in patients undergoing BCS is to eliminate microscopic foci that may remain in the breast. While the risk of recurrence was 28% in patients who did not receive RT after BCS, it was 13% in those who received RT [1]. Similarly, in cases with positive hormone receptors after BCS, the long-term risk of recurrence was reported to be 24% with only adjuvant tamoxifen and 9.7% with MKC+TMRT+tamoxifen [2].

Even in the presence of favorable prognostic factors such as low grade, small tumor, and adequate surgical margin after BCS, the rate of local recurrence with BCS alone rises above 10%. In the ECOG-ACRIN E5194 study, which is a prospective phase II study, local recurrence rates were reported as 14.4% in patients with tumor diameter <2.5 cm, low-intermediate grade and negative surgical margins, and 24.6% in high-grade patients who underwent only BCS and were followed up for 12 years [3]. In recent years, studies have been carried out to plan DCIS treatment in the light of clinical prognostic factors as well as molecular and genetic factors. However, adjuvant TMRT is still accepted as the standard approach in all cases with BCS. In these patients, 45-50 Gy radiotherapy (RT) is applied to the whole breast in conventional fractions. The application of additional doses to the tumor bed is still controversial.

Radiotherapy in Early Stage Invasive Breast Cancer

Whole breast Radiotherapy after Breast Conserving Surgery (BCS)

Adjuvant radiotherapy is recommended as standard for patients diagnosed with invasive breast cancer and undergoing BCS. Thus, it is aimed to destroy the tumor cells that may be left behind after surgery, to reduce the risk of recurrence of the disease and to increase the survival rate. In prospective randomized clinical studies comparing BCS alone and TMRT after BCS, TMRT has been shown to significantly reduce loco-regional recurrence and breast cancer-related mortality [4, 5].

As a standard, TMRT is administered at a daily fraction of 1.8-2 Gy, 45-50 Gy for 5 weeks, 5 days a week. This is called conventional fractionation. Another treatment option is the "hypofractionated" radiotherapy (HFRT) scheme. The scheme used in HFRT today is a total dose of 40-42.5 Gy completed in 3-3.5 weeks at a fractionated dose of 2.66-2.67

Gy. HFRT is preferred because it is completed in a short time and especially due to its low acute toxicity rate [6]. In a meta-analysis of phase III randomized clinical trials comparing HFRT with conventional RT, HFRT was found to be median safe [7]. **H**owever, there is not enough data yet for HFRT in cases <40 years old, undergoing neo-adjuvant chemotherapy (CT) and requiring lymphatic irradiation.

With the additional dose of RT (boost) applied to the tumor bed after TMRT, the risk of recurrence and thus the rate of subsequent mastectomy is reduced, but this does not contribute to overall survival (OS). The most significant reduction in local recurrence with additional dose radiotherapy applied to the tumor bed has been shown in high-grade patients with adequate surgical margins and ≤50 years of age [8]. Surgical margin positivity results in high local recurrence even if an additional dose is applied to the tumor bed. Therefore, if surgical margin negativity cannot be achieved in BCS, mastectomy is recommended.

Additional dose of radiotherapy to the tumor bed is administered as a dose of 10-16 Gy in 2 Gy fractions with a safety margin of 1-2 cm. If the daily dose is kept to 2.5 Gy, the total dose is generally about 10 Gy (4x2.5 Gy).

Partial Breast Radiotherapy (PMRT)

In the treatment of early-stage invasive breast cancer, 2/3 of local recurrences occur around the cavity where the primary tumor was removed (true recurrence), and 1/3 occur in other quadrants (new primary tumor) [9]. This fact, observed in the long-term results of prospective clinical studies, has led to the emergence and application of the concept of PMRT. In PMRT, only radiotherapy (boost) to the tumor bed is applied with a certain safety margin, from smaller areas and at a higher fraction dose compared to TMRT. Patient selection is very important in this method, and it is recommended only in patients with a low risk of recurrence [10]. According to the recommendations of ASTRO (American Society of Radiation Oncology), PMRT is recommended only for cases with all the following features: ≥50 years old, no BRCA mutation, small diameter (≤2cm), positive ER, lymph node (LN) metastasis and lymphovascular vessel invasion (LVI), negative surgical margins (≥2 mm), unifocal tumor, and not receiving neoadjuvant CT (NACT) [11].

PMRT can be applied with different techniques such as interstitial brachytherapy (BRT), intracavitary BRT, intraoperative RT (IORT), 3-dimensional conformal RT (3DCRT), and intensity modulated RT (IMRT). The total duration of treatment in this

treatment is usually between 1-3 weeks. In IORT applications, a dose of 20-21 Gy is applied with a single fraction of electron beams or low-energy X-rays with an operating room-mounted RT device during surgical intervention.

Radiotherapy in locally advanced breast cancer

Adjuvant Radiotherapy After Mastectomy

Adjuvant RT is routinely recommended in the presence of T3-T4 tumors, >3 LN metastases, positive surgical margins, and skin-fascia involvement after mastectomy [12-13]. However, in the presence of T1-2 tumor and 1-3 LN metastases, the need for adjuvant RT is still being discussed, especially because of the risk of treatment-related side effects. In phase III studies, a significant increase in loco-regional control and survival was demonstrated with adjuvant RT in this group of patients [14-16]. In the "National Comprehensive Cancer Network" (NCCN) guideline, the RT level of evidence is recommended as high in the presence of 1-3 LN metastases [17]. In the Saint Gallen consensus guideline, it is recommended to look for additional prognostic factors such as triple negative breast cancer or no ALND in the presence of 1-3 LN metastases [12].

In RT after mastectomy, while adequate and homogeneous radiation dose is given to the chest wall, the surrounding normal tissues and organs, especially the heart, lungs and contralateral breast, should be protected. With or without breast reconstruction, the skin and chest wall are defined as the target volume and 45-50 Gy is applied in conventional fractions.

Radiotherapy after Neoadjuvant Chemotherapy (NACT)

TMRT is essential in cases with BCS after NACT. The decision for radiotherapy in cases undergoing a mastectomy is made according to the extent of the residual disease and the clinical stage before LT. The presence of LN metastases in the pathology specimen, especially after LT, is the most important prognostic factor [18]. Similarly, in the presence of Stage IIB and III disease at the time of diagnosis, adjuvant PMRT provides a significant increase in disease-free survival [19].

In patients diagnosed with locally advanced breast cancer (LABC) at the time of diagnosis, the recurrence-free survival rate is low with surgery alone, even if a complete pathological response is achieved after neoadjuvant chemotherapy. In the American National Cancer database, an increase in overall survival has been shown with adjuvant RT in patients diagnosed with LABC (20). The latest Saint Gallen consensus guideline recommends PMRT in the presence of Stage IIB (cT3N0M0) and triple negative disease, even if there is a

pathological total response to chemotherapy [12].

Regional Nodal Irradiation (RNI)

Sentinel lymph node biopsy (SLNB) is a standard method for the evaluation of the axilla in breast cancer patients with clinically negative axilla. In the AMAROS study, in which patients with sentinel lymph node metastases were randomized to axillary dissection (ALND) or axillary RT arms and followed up for 10 years, no recurrence or survival difference was found between the two treatment arms. However, lymphedema rates were higher in the ALND arm [21]. Today, lymphatic irradiation to the axilla is routinely recommended in all cases with metastasis in SLNB and cases that ALND cannot be done. There is no consensus on RNI in ALND cases. The RNI decision is made by considering factors such as the presence of additional lymph node metastases detected after ALND, the stage of the primary tumor, accompanying lymphovascular invasion in the tumor, the presence of extracapsular invasion in the metastatic lymph node, molecular subtype, and patient age.

In the presence of ≥4 LN metastases in the axilla in ALND patients, routine RNI is recommended in addition to TMRT or chest wall radiotherapy. RNI includes infraclavicular, supraclavicular, and mammary interna (MI) lymph nodes. In cases where ALND is not performed or has been inadequately performed (<10 LN removed), or in cases with extensive LN involvement, the entire axilla should be irradiated. The radiation dose is 45-50 Gy in conventional fractions. If 1-3 LN metastases are detected after ALND, it is controversial whether RNI should be performed. In phase III studies on this subject, RNI has shown a decrease in the risk of local-regional recurrence, an increase in disease-free survival, and a decrease in the rate of death from breast cancer after 15 years of follow-up [22-24]. Today, routine RNI is recommended in cases with 1-3 LN metastases in the presence of other high-risk factors. These high-risk factors are counted as high histological grade, T3-T4 tumor, hormone receptor negativity, triple negative or HER-2 (+) molecular subtypes, presence of lymphovascular invasion, or residual disease in the axilla after neoadjuvant chemotherapy [11-12, 25].

Technical

RT of a patient with breast cancer begins with the evaluation of the patient in the radiotherapy clinic and continues with computed tomography (CT) in the treatment position

after appropriate immobilization (Figure 1). Target volumes and surrounding normal organs are contoured on the CT images taken (Figure 2). After treatment planning (Figure 3) and quality control study, the patient is taken to treatment. In the past, RT was applied with the 2D technique, but today, with the development of new radiotherapy devices and planning systems, it is possible to give minimal radiation to the surrounding normal tissues while applying homogeneous and high radiation doses in target volumes.

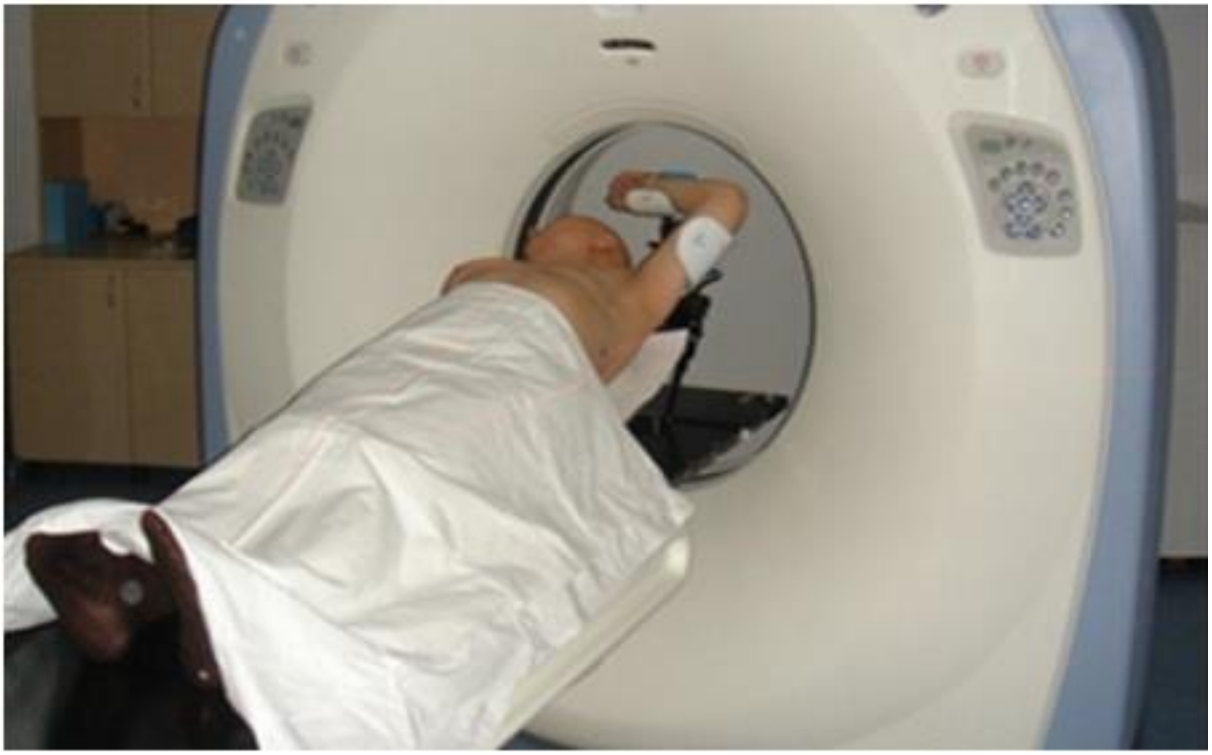


Figure 1. Simulation with Computed Tomography (CT) in a Patient Planned for Radiotherapy

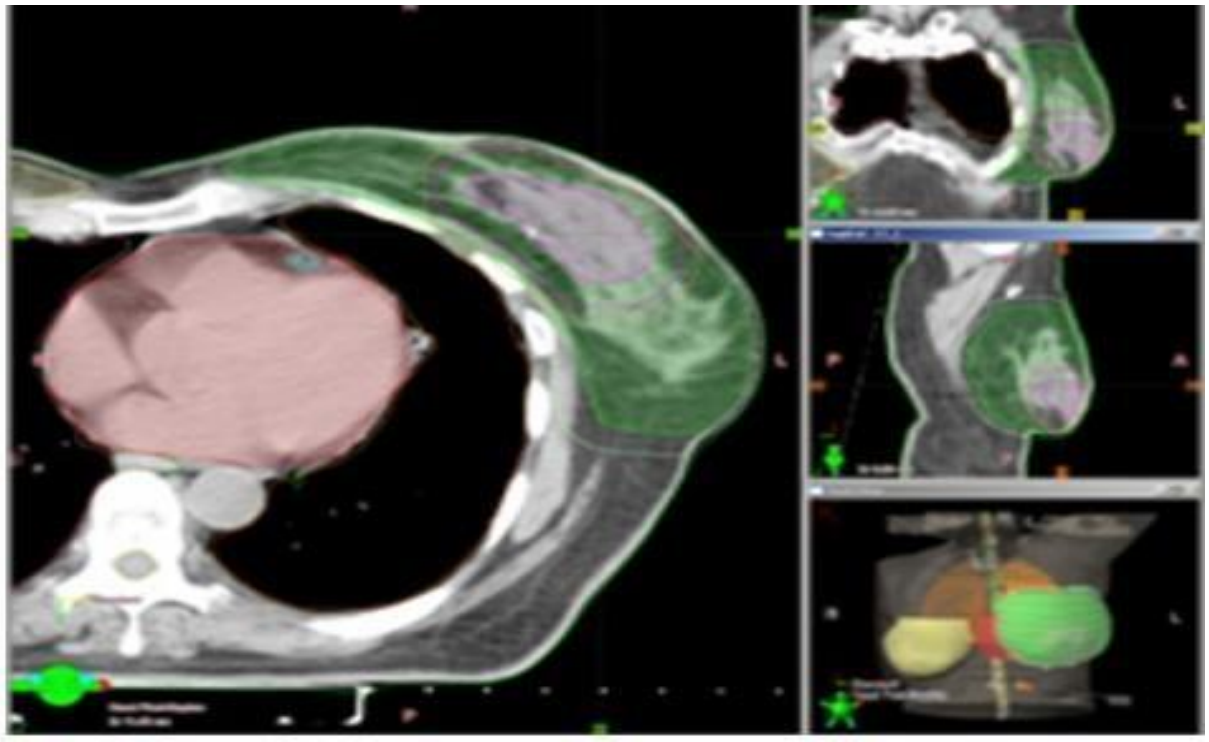


Figure 2. Drawing of Target Volume and Surrounding Normal Tissues and Organs on Computed Tomography (CT) Sections

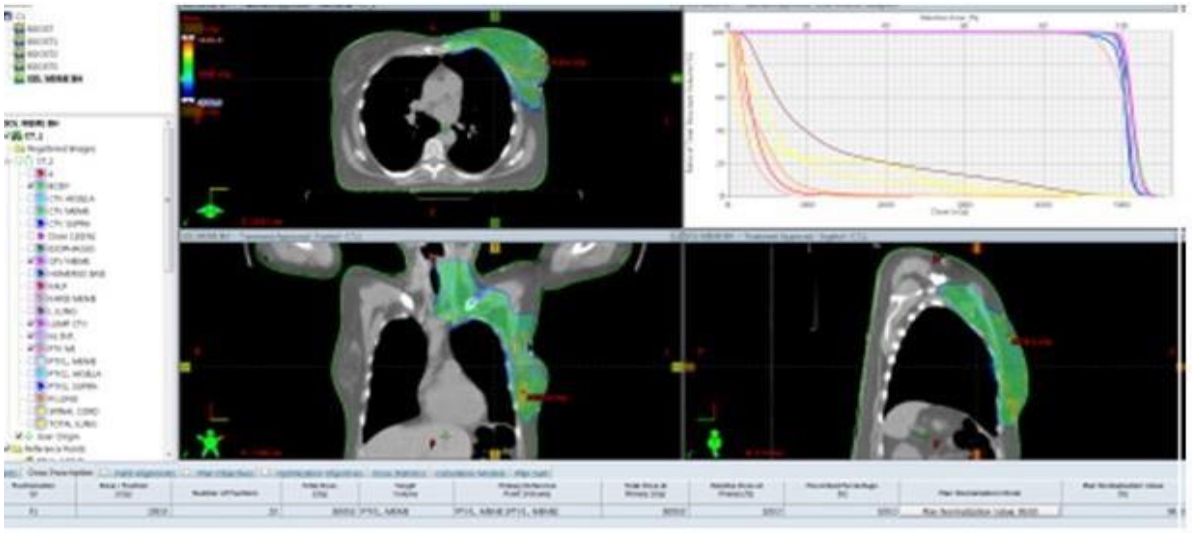


Figure 3. Treatment Planning and Dose Volume Histogram

RESOURCES

1. *Correa C, McGale P, et al. Early Breast Cancer Trialists' Collaborative Group, Overview of the randomized trials of radiotherapy in ductal carcinoma in situ of the breast. J Natl Cancer Inst Monogr. 2010;(41):162-177.*

2. *Kirsty E. Stuart, Nehmat Houssami and John Boyages. Long-term outcomes of ductal carcinoma in situ of the breast: a systematic review, meta-analysis and meta-regression analysis. BMC Cancer. 2015: 15: 890.*

3. *Solin LJ, Gray R, Hughes LL et al. Surgical Excision Without Radiation for Ductal Carcinoma in Situ of the Breast: 12-Year Results From the ECOG-ACRIN E5194 Study. J Clin Oncol. 2015;33(33):3938-44.*

4. *Clarke M, Collins R, Darby S, et al. Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. Lancet. 2005;366(9503):2087-2106.*

5. *Early Breast Cancer Trialists' Collaborative Group, Darby S, McGale P, et al. Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10,801 women in 17 randomised trials. Lancet. 2011;378(9804):1707-1716.*

6. *Smith BD, Bellon JR, Blitzblau R, et al. Radiation therapy for the whole breast: Executive summary of an American Society for Radiation Oncology (ASTRO) evidence-based guideline. Practical Radiation Oncology 2018; 8:145-152.*

7. *Andrade TRM, Fonseca MCM, Segreto HRC, et al. Meta-analysis of long-term efficacy and safety of hypofractionated radiotherapy in the treatment of early breast cancer. The Breast. 2019;48:24-31.*

8. *Bartelink H, Maingon P, Poortmans P, et al. Whole-breast irradiation with or without a boost for patients treated with breast-conserving surgery for early breast cancer: 20-year follow-up of a randomised phase 3 trial.Lancet Oncol. 2015 Jan;16(1):47-56.*

9. *Mannino M, Yarnold J. Accelerated partial breast irradiation trials: diversity in rationale and design. Radiother Oncol. 2009;91(1):16-22.*

10. *Polgar C, Van Limbergen E, Potter R, et al. Patient selection for accelerated partial-breast irradiation (APBI) after breast-conserving surgery: recommendations of the Groupe Europeen de Curietherapie-European Society for Therapeutic Radiology and Oncology (GEC-ESTRO)*

breast cancer working group based on clinical evidence (2009). Radiother Oncol. 2010;94(3):264-273.

11. *Correa C, Harris EE, Leonardi MC, et al. Accelerated Partial Breast Irradiation: Executive summary for the update of an ASTRO Evidence-Based Consensus Statement. Pract Radiat Oncol. 2017;7(2):73-79.*

12. *Balica M, Thomssenb C, Würstlein R, et al. St. Gallen/Vienna 2019: A Brief Summary of the Consensus Discussion on the Optimal Primary Breast Cancer Treatment. Breast Care 2019; 14:103–110.*

13. *Recht A, Comen E.A., Fine R.E. Postmastectomy Radiotherapy: An American Society of Clinical Oncology, American Society for Radiation Oncology, and Society of Surgical Oncology Focused Guideline Update. Practical Radiation Oncology. 2016; 6: 219-34.*

14. *Overgaard M, Jensen MB, Overgaard J, et al. Postoperative radiotherapy in high-risk postmenopausal breast-cancer patients given adjuvant tamoxifen: Danish Breast Cancer Cooperative Group DBCG 82c randomised trial. Lancet. 1999;353(9165):1641-1648.*

15. *Ragaz J, Olivotto IA, Spinelli JJ, et al. Locoregional radiation therapy in patients with high-risk breast cancer receiving adjuvant chemotherapy: 20-year results of the British Columbia randomized trial. J Natl Cancer Inst. 2005;97(2):116-126*

16. *Overgaard M, Hansen PS, Overgaard J, et al. Postoperative radiotherapy in high-risk premenopausal women with breast cancer who receive adjuvant chemotherapy. Danish Breast Cancer Cooperative Group 82b Trial. N Engl J Med. 1997;337(14):949-955.*

17. *NCCN Clinical Practice Guidelines in Oncology: Breast Cancer. Version 3. 2019. NCCN.org*

18. *Mamounas EP, Anderson SJ, Dignam JJ, et al. Predictors of locoregional recurrence after neoadjuvant chemotherapy: results from combined analysis of National Surgical Adjuvant Breast and Bowel Project B-18 and B-27. J Clin Oncol.*

19. *2012;30(32):3960-3966.*

20. *Huang EH, Tucker SL, Strom EA, et al. Postmastectomy radiation improves local-regional control and survival for selected patients with locally advanced breast cancer treated with neoadjuvant chemotherapy and mastectomy. J Clin Oncol. 2004;22(23):4691-4699.*

21. *Rusthoven CG, Rabinovitch RA, Jones BL, et al. The impact of postmastectomy and regional nodal radiation after neoadjuvant chemotherapy for clinically lymph node-positive breast cancer: a National Cancer Database (NCDB) analysis.Ann Oncol. 2016;27(5):818-27.*

22. *EJ Rutgers, M Donker, C Poncet, et al. Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer patients: 10 year follow up results of the EORTC AMAROS trial*

(EORTC 10981/22023): 2018 San Antonio Breast Cancer Symposium; December 4-8, 2018; San Antonio, Texas, Abstract GS4-01: DOI: 10.1158/1538-7445.SABCS18-GS4- 01 Published February 2019.

23. *Whelan TJ, Olivotto IA, Parulekar WR, et al. Regional Nodal Irradiation in Early- Stage Breast Cancer.N Engl J Med. 2015;373(4):307-16.*

24. *Poortmans P, Collette S, Struikmans H et al. Fifteen-year results of the randomised EORTC trial 22922/10925 investigating internal mammary and medial supraclavicular (IM-MS) lymph node irradiation in stage I-III breast cancer. Journal of Clinical Oncology 36, no. 15 suppl (May 20, 2018) 504-504.*

25. *Dodwell D, Taylor C, McGale P, et al. Regional lymph node irradiation in early stage breast cancer: An EBCTCG meta-analysis of 13,000 women in 14 trials. Abstract GS4- 02: Proceedings of the 2018 San Antonio Breast Cancer Symposium; 2018 Dec 4-8; San Antonio, TX. Philadelphia (PA): AACR; Cancer Res 2019;79(4 Suppl): Abstract nr GS4-02.*

26. *Budach W, Kammers K, Boelke E and Matuschek C. Adjuvant radiotherapy of regional lymph nodes in breast cancer - a meta-analysis of randomized trials.Radiat Oncol. 2013*

SECTION 6

INTERNATIONAL ORGANIZATIONS AND ACTIVITIES

6. INTERNATIONAL ORGANIZATIONS AND ACTIVITIES

6.1. WHO: World Health Organization

Cancer is the second most common cause of death globally. It caused the deaths of approximately 9.6 million people in 2018. In other words, one out of every 6 deaths in the world is due to cancer.

From another perspective, the cancer burden continues to grow globally. It places enormous physical, emotional, and financial pressures on individuals, families, communities, and health systems.

In WHO reports and meetings, it is clearly stated that our country is in a good place in the fight against cancer, both in prevention and in early diagnosis and treatment activities. However, our Presidency continues to work with all its determination for the ways and cooperation to be taken in the fight against this disease, which has great pressure and effects on health systems and society.

In October 2011, the "Cervical Cancer Prevention Meeting" was held in Istanbul with the participation of 111 experts and managers from 42 countries, as well as 7 cooperative organizations, under the chairmanship of WHO. In the said meeting, the progress and cooperation of our Ministry in the context of the subject were praised, and the foundations of future cooperation in the fight against cervical cancer were laid.

International Commission on Non-Ionizing Radiation Protection, International Telecommunication Union (ITU) established by the World Health Organization and made by the governments of countries and international independent research agencies (ICNIRP). Since 2013, participation has been made at the level of the Ministry of Health in the "International Electromagnetic Fields" Project, which is carried out together with the International Electrotechnical Commission (IEC).

In 2018, the Non-Communicable Diseases Prevention and Control Investment Justifications report was prepared in cooperation with WHO to show the financial burdens of non-communicable diseases, especially cancer, and the cost-effectiveness of the fight.

6.2. IARC- International Agency for Research on Cancer

The International Agency for Research on Cancer was established in May 1965 as an extension of WHO at the 18th World Health Assembly with the support of the Federal Republic of Germany, France, Italy, America and England. IARC, whose main office is in Lyon, France, has 27 member countries, including Turkey.

The task of IARC is to identify the causes of cancers in humans and the functioning of carcinogenic mechanisms, to support and organize studies conducted for this purpose, and to develop scientific strategies to control cancer. For this reason, IARC, which serves as a fully independent organization, has no industrial support or relationship. It conducts all kinds of cancer research on a global scale with the support of member countries and provides scientific information at the highest level on the issues that the public needs.

The "European Code Against Cancer", first published by IARC in 1987, was revised and its 4th version was announced in 2014 in order to focus on what individuals can do to reduce the risk of cancer in themselves and their relatives and to prevent cancer.

In this code, which aims to prevent cancer with a healthier life throughout Europe, it is emphasized that the main element of the fight against cancer is cancer prevention and healthy living strategies. Detailed scientific reports created by syntheses of all researches in the world about each of the cancer codes are also regularly published by IARC. (See Section: 3.2.8 “European Code Against Cancer” 12 Articles in the European Union 4. Cancer Control Code.)

Our Department, which is in close cooperation with the IARC, is one of the few countries that participate in the decision stages by closely following the scientific discussions on cancer-related issues that occupy the world agenda and by actively assigning its own scientists to these discussions. In addition, what needs to be done regarding cancer in our country is evaluated and clarified by the most important scientific committees in the world.

T.R. Apart from the ongoing studies between the Ministry of Health General Directorate of Public Health, Cancer Department, and IARC, it is planned to carry out cooperation and studies that are important for the coming years on many issues such as

environmental cancer factors and nutrition that are currently discussed.

6.2.1. IARC-Western Asia, Central Asia, and Northern Africa Regional Center for Cancer Registry ARC-İZMİR HUB

İzmir Cancer Registry Center has been designated as "IARC Regional Center-HUB" within the framework of the Global Initiative for Cancer Registry Development (GICR-Global Initiative for Cancer Registry Development) initiated by the World Health Organization/International Agency for Cancer Research (WHO/IARC). It has been commissioned to provide training, technical support, and scientific consultancy in the development of cancer registry and cancer registry centers in 30 countries in Asia, the Middle East, and North Africa.

Looking at the historical process of Izmir Cancer Registry; It was established in 1992 as Turkey's first community-based cancer registry center and published its first data in 2001. Following the IARC Mumbai Hub established in India, it officially became the Regional HUB of IARC on 9 October 2013, with a protocol signed between the Public Health Agency of Turkey and the International Agency for Research on Cancer/World Health Organization (IARC/WHO).

The purpose of the HUB is to be a problem-solving center for the countries in the cancer registry hub region (***North Africa****: Algeria, Egypt, Libya, Morocco, South Sudan, Sudan, Tunisia, Western Sahara.* ***Western Asia:*** *Armenia, Azerbaijan, Bahrain, Cyprus, Georgia, Iraq, Israel, Jordan, Kuwait, Lebanon, Oman, Qatar, Saudi Arabia, Palestine, Syria, Turkey, United Arab Emirates, Yemen* ***Central Asia:*** *Kazakhstan, Kyrgyzstan, Tajikistan, Turkmenistan, Uzbekistan)*. In addition to this, it also provides services in the fields of support, advocacy, consultancy, and training related to cancer registry, and to provide communication between IARC and hub countries.

The consultancy activities of IARC İzmir HUB started in October 2013, 81 basic and advanced training activities were organized, and around 420 cancer registry center personnel and managers received training in these activities. Seven educational visits were made to Izmir Cancer Registry Center (TRNC, United Arab Emirates, Azerbaijan, Kyrgyzstan, Jordan, Palestine, Iraq). İzmir HUB team made many visits to the Hub region for basic and advanced training, support and audit visits to cancer registry centers,

consultancy, technical support and training. During the visits to the TRNC, Morocco, Palestine, Georgia, Kyrgyzstan, Lebanon, Egypt, Uzbekistan, Iraq, Syria, Azerbaijan, Oman and Tunisia, suggestions were made to establish or develop a cancer registry center.

6.3. European Union Scientific Commission

Cancer, which is rapidly increasing among the causes of death in Europe, is seen as one of the biggest problems of the twenty-first century. Global studies in the fight against cancer have been going on since the 1970s. Intense collaboration between the medical, technological and industrial communities is indispensable in this fight. Cancer-related research and innovation are, and will continue to be, among high priorities today.

Within the scope of the common fight against cancer carried out worldwide, a report was published in June 2014 by the European Union Cancer Control Scientific Committee, of which our Department is a member, and joint strategies were determined.

It is possible to summarize the strategies included in the commission report published on 3 June 2014 and targeted to be implemented by 2013 as follows:

1. The report highlights two important steps in the fight against cancer: 1-Prevention, 2) Cancer Screening/Early Diagnosis. In the report, in which it was stated that the most important preventable factors causing cancer formation, especially the use of tobacco products, obesity, low consumption of fruits and vegetables, alcohol consumption and physical inactivity, it was stated that the fight against these preventable causes would prevent the formation of cancer by 30%.
2. In the early diagnosis stage, especially breast, cervix and colorectal cancer screenings have an important place. It has been stated that if a 100% coverage rate is achieved in cervical cancer screenings, there will be a decrease of more than 94% in the loss of life years due to this cancer.
3. It has been stated that if cancer screenings (breast, cervix and colorectal) become widespread in member countries and reach the expected rates, the annual number of new cancer diagnoses in these countries will decrease by half. For this reason, it has been suggested to aim for 100% coverage in breast, colorectal and cervical cancer screenings, and to carry out activities in a way that includes executing major media campaigns of member countries in reaching the target.
4. It is recommended that measures to be taken against infectious factors that cause

cancer, such as the HPV virus, should be evaluated in terms of an effective fight against cancer.

5. The importance of palliative care services aimed at increasing the quality of life for people diagnosed with incurable-advanced cancer was emphasized. It has been stated that member countries are at different stages in terms of palliative care services, and international common standards can be achieved if they act in cooperation and transfer their experiences to each other in this respect.
6. It is necessary to increase research in the field of cancer and to establish international cooperation areas in this field.
7. A cancer registry needs to be developed in member countries, as it is very important for countries to prepare status reports in the fight against cancer, both in determining country policies and in making international evaluations.

6.4. UICC-Union for International Cancer Control

The International Union for Cancer Control (UICC) was established in 1933 with the aim of reducing the cancer burden on a global scale and ensuring that cancer control continues to be a priority on the world's health and development agenda. Our country has been a member of the union since 1969. The Association is the world's largest cancer-fighting non-governmental organization with more than 2000 members in more than 170 countries. These members include the world's major cancer associations, ministries of health, cancer institutes, research institutes, treatment centers, and patient groups. It works in close cooperation with different international health organizations (World Health Organization-WHO, International Agency for Research on Cancer-IARC, International Cancer Treatment Action Program-PACT). UICC is also one of the founding members of the “Joining Platform Against Non-Communicable Diseases” and the group is a global civil society comprising 1150 organizations in 173 countries.

The International Agency for Prevention of Cancer (UICC) organizes awareness events at the global level in cooperation with relevant institutions and organizations on World Cancer Day (4 February) and publishes them on its website.

UICC expressed its goals at important meetings such as the World Cancer Leaders Summit, World Cancer Congress, and World Cancer Day:

- Develop specific time-bound targets and indicators to measure national implementation of policies and approaches to prevent and control cancer
- Increasing the priority given to cancer in the global health and development agenda
- and to encourage a global response to cancer and

continues to work in this direction.

The World Leaders' Summit Meeting was held in Kazakhstan on 15-17 October 2019 and our Department participated. International Organization for Cancer Control (UICC), World Health Organization (WHO), International Atomic Energy Agency (IAEA), International Agency for Research on Cancer (IARC), and Kazakhstan Institute of Oncology and Radiology (KazIOR) attended the meeting.

6.5. Meetings of the US Cancer Institute and World Cancer Leaders

It was supported by the idea that a commission was needed to conduct research, support, and create strategic plans in order to be successful in the fight against cancer in the United States in 1927.

It was declared by the US Senate as an independent research institute as of the date of August 5, 1937. On July 1, 1944, the National Cancer Institute became a part of the National Institute of Health and became an important institution in the fight against cancer, supported by the law by the government, and its responsibilities were gradually expanded.

Today, the National Cancer Institute (NCI) is an institute affiliated with the National Institute of Health (NIH), one of the eleven agencies of the United States Department of Human and Health Services. Cancer causes, prevention, diagnosis, and treatment research are carried out by this institute, and the information and data obtained are made available to the public. It also leads the research of new drugs developed for cancer treatment.

Cancer leaders of developed countries such as Australia, Canada, China, France, Germany, Hong Kong, Italy, Japan, Mexico, Netherlands, England, USA and Turkey participate in the "International Meetings of Developed Countries Supporting Cancer Research" organized by NCI.

6.6. IPRI: The International Prevention Research Institute

IPRI is an independent institution that carries out international prevention studies and has been operating since 2009. It conducts research on important health issues and publishes international guidelines with the data obtained. Diabetes, cancer and disease screenings are among the important topics of their studies. The studies are evaluated together and compilations are published for each subject.

In addition to the scientific studies carried out, IPRI organizes various meetings such as international Cancer Institute executive meetings.

IPRI is an academic, problem-solving institute working closely on various projects with a number of Senior Research Fellows from different corners of the world.

In the book "Cancer in the World Report 2013" published by IPRI, our country also took part in the cancer control program, and even its cancer control program was considered among the best programs at the World Cancer Leaders Summit.

6.7. APOCP: The Asian Pacific Organization for Cancer Prevention

Asia Pacific Countries Cancer Prevention Organization (APOCP) is an impartial organization established in 2000 to develop cancer preventive activities among Asian Pacific Countries and to carry out international joint studies on other cancer issues. Among the main objectives of this organization are to provide opportunities for expert researchers to carry out international studies and to share the results of the studies on a common platform.

The fight against cancer is global. In addition, interventions require an integrated approach. For this reason, our Department's regular and continuous participation in international cooperation calls is important in terms of being a part of international scientific studies and research, closely following the announced innovations, monitoring and evaluating the practices, and it tries to carry out this task successfully.

6.8. EUROMED Cancer Network Project

The EUROMED Cancer Network project is the Cancer Network Project that aims to support the development of cancer early detection and screening policies in Mediterranean countries outside the EU. EUROMED Workshop is an organization of the WHO Cancer Early Diagnosis and Screening Collaboration Center, which is part of the EUROMED Network, in cooperation with the Paris Cancer Institute and the Mediterranean Union. In this workshop, it was aimed to share the ongoing early diagnosis and screening activities of countries and to develop future cooperation as the EUROMED Cancer Screening Network. Our country is an important member of the EUROMED Cancer Screening Network.

With the workshop held in Morocco-Marrakesh on 19-20 June 2019, cooperation was developed by sharing the screening activities with other countries, especially the HPV-DNA Screening program carried out at the national level in our country, which is set as an example in the world.

IARC / WHO is leading the initiative to create a global repository of data on cancer screening programs around the world. The project is called Cancer Screening in 5 Continents (CanScreen5).

The aim of the CanScreen5 project is to encourage and support countries to collect and use cancer screening data for program evaluation and quality improvement.

6.9. SEEHN: South-Eastern Europe Health Network

WHO Europe contributes to restructuring efforts in Southeast European countries in the WHO European Region through its work with the South-eastern Europe Health Network (SEEHN). SEEHN is a political and institutional platform established by Albania, Bosnia and Herzegovina, Bulgaria, Croatia, Montenegro, Republic of Moldova, Romania, Serbia, and the Republic of North Macedonia to promote peace, reconciliation, and health in the region.

Within the scope of the European Commission Technical Assistance and Information Exchange (TAIEX) Mechanism, the multi-country workshop on "Increasing Colorectal Cancer Screening Programs in the Southeast European Health Network Countries" was held in Podgorica, Montenegro on 12-13 December 2019 in cooperation with the Southeast Europe Health Network, Department of Cancer from our Ministry participated and made two presentations on “Colorectal Cancer Screening Organization and Practice in Turkey” and

“Health Information Systems Supporting Colorectal Cancer Screening in Turkey”.

6.10. Albanian Embassy - MÜSİAD

Between 31 March and 8 April 2018 in Albania, a total of 3 days of screening service was provided to the Albanian people, which has deep-rooted historical political relations with our country, with our mobile cancer screening tool (cervical cancer screening with HPV-DNA test and breast cancer screening). With the support of the Independent Industrialists' and Businessmen's Association (MUSIAD), this program aims to raise awareness for the Albanian people.

SECTION 7

CANCER LOAD IN THE WORLD AND IN TURKEY

7. Cancer Burden in the World and in Turkey

Undoubtedly, cancer is one of the world's leading health problems. Because when we look at the causes of death worldwide, it was published in the World Cancer report of 2012 by IARC that deaths due to cancer were in the first place with 7.87 million in 2011. This is followed by ischemic heart diseases with 7.02 million and strokes with 6.25 million (Figure 1).

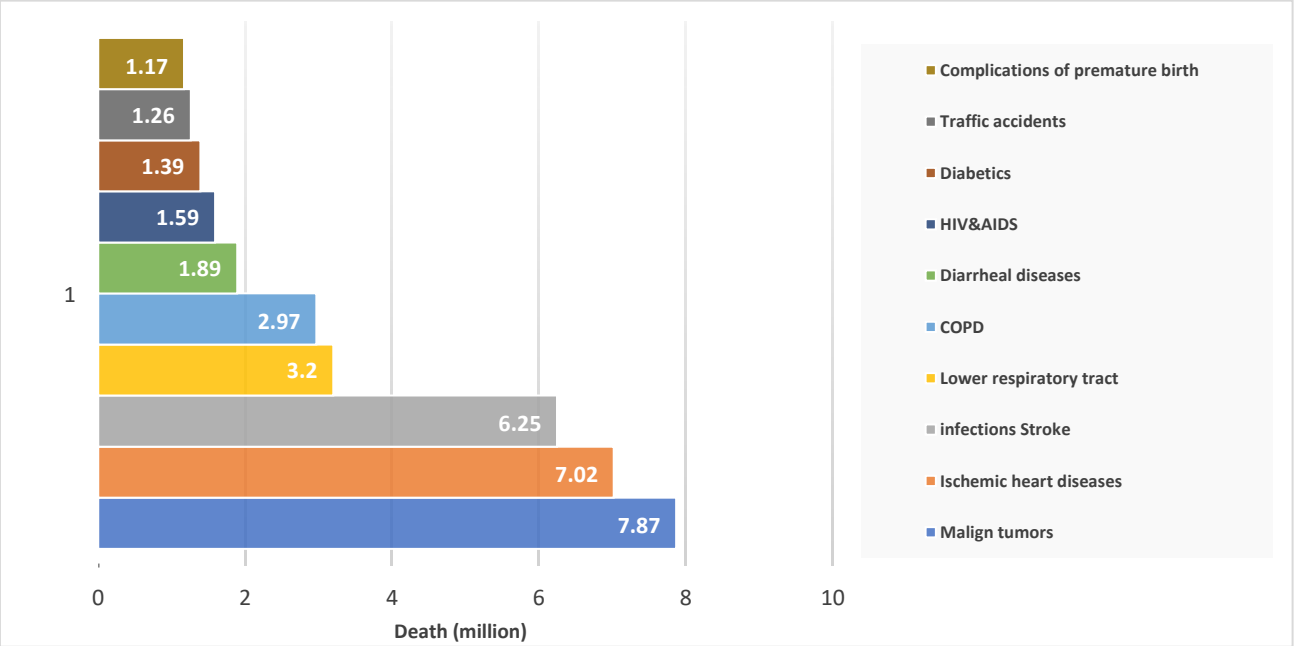


Figure 1. Causes of Death in the World, 2011 (World Cancer Report, 2014)

According to the statistics published by the World Health Organization International Agency for Research on Cancer Control ("IARC, International Agency for Research on Cancer Control") in 2018, 18 million people in the world are diagnosed with cancer every year. The number of people who die of cancer each year is 9.6 million. According to the World Health Organization (WHO) data, in 91 of 172 countries in 2015, "cancer" was reported as the first or second cause of death in deaths up to the age of 70. In Turkey, on the other hand, it is estimated that 210,537 cancer cases are seen every year according to WHO and IARC figures, and cancer deaths are estimated to be 116,710. According to the 2016 data obtained from the Ministry of Health, it is estimated that there are 176,934 cases. According to TUIK 2017 data, 81,527 people died from cancer

in Turkey, accounting for 19.6% of all deaths, and ranks second after circulatory system diseases, which is the first cause of death, with 39.7% **(Table 1).**

Table 1. Causes of Death in 2017 Turkish Statistical Institute (TSI)

	2016 [(r)]		**2017**	
	number	(%)	number	(%)
Circulatory system diseases	166.069	39.5	165.323	39.7
Benign and malignant tumors (malignant and benign neoplasms)	81.647	19.4	81.527	19.6
Respiratory system diseases	49.295	11.7	49.855	12.0
Diseases related to endocrine, nutrition and metabolism	20.731	5.0	20.110	4.8
Nervous system and sensory organs diseases	20.220	4.8	20.504	4.9
External causes of injury and poisoning	21.473	5.1	18.901	4.5
Other (infectious and parasitic diseases, mental and behavioral disorders, diseases of the musculoskeletal system and connective tissue, etc.)	60.754	14.5	60.661	14.5
Total	**420.189**	**100,0**	**416.881**	**100,0**

Figures in the table may not total due to rounding.

2016[(r)] data has been revised due to the updating of administrative records.

Size of Cancer in the World

The most widely used cancer figures in the world are the statistics and mortality figures of 36 cancer types in 185 countries in 20 regions of the world, published by IARC in 2002, 2008, 2012 and finally reported in 2018.

Of the cancer cases that exceeded 18 million in 2018, nearly 50% are in Asia, 25% are in Europe, and 20% are in the Americas. Considering the incidence, it is seen that the highest incidence is in Oceania and North America. **(Table 2)**

In Table 3, all cancers seen in the world in 2018 are listed. Lung and breast cancers occupy the first place with numbers exceeding two million. Age-standardized cancer incidences were found to be 218.6 per 100 thousand population in men and 182.6 in women in 2018. Since both genders are considered together, the age-standardized cancer incidence in 2018 is 197.9 per hundred thousand for the world. Looking at the cumulative risk, it is calculated that one out of every eight men and one

out of every 10 women will develop cancer in their lifetime. Calculations made in high-income countries show that one-third to two-fifths of cancer can be prevented in total by protecting healthy living and environmental exposures.

Table 2. Distribution of Cancer According to Continents, IARC 2018

	number	Incidence	%
Asia	8,750,932	164,5	48.4
Europe	4,229,662	281,5	23.4
North America	2,378,785	350,2	13.2
Latin America and the Caribbean	1,412,732	189,6	7.8
Africa	1,055,172	129,7	5.8
Oceania	251.674	418,8	1.4.

Table 3. Cancer Incidences and Deaths in 2018 in the World

IARC, 2018

Cancer	**Number of cases (%)**	**Number of deaths (%)**
Lung	2,093,876 (11.6)	1,761,007 (18.4)
Breast	2,088,849 (11.6)	626,679 (6.6)
Prostate	1,276,106 (7.1)	358,989 (3.8)
Colon	1,096,601 (6.1)	551,269 (5.8)
Non-melanoma skin	1,042,056 (5.8)	65,155 (0.7)

Stomach	1,033,701 (5.7)	782,685 (8.2)
Liver	841,080 (4.7)	781,631 (8.2)
Rectum	704,376 (3.9)	310,394 (3.2)
Esophagus	572,034 (3.2)	508,585 (5.3)
Cervix uteri	569,847 (3.2)	311,365 (3.3)
Thyroid	567,233 (3.1)	41,071 (0.4)
Bladder	549,393 (3.0)	199,922 (2.1)
Non-Hodgkin lymphoma	509,590 (2.8)	248,724 (2.6)
Pancreas	458,918 (2.5)	432,242 (4.5)
Leukemia	437,033 (2.4)	309,006 (3.2)
Kidney	403,262 (2.2)	175,098 (1.8)
Uterus Corpus	382,069 (2.1)	89,929 (0.9)
Lip, oral cavity	354,864 (2.0)	177,384 (1.9)
Brain, nervous system	296,851 (1.6)	241,037 (2.5)
Over	295,414 (1.6)	184,799 (1.9)
Skin melanoma	287,723 (1.6)	60,712 (0.6)
Gall bladder	219,420 (1.2)	165,087 (1.7)
Larynx	177,422 (1.0)	94,771 (1.0)
Multiple myeloma	159,985 (0.9)	106,105 (1.1)
Nasopharynx	129,079 (0.7)	72,987 (0.8)
Oropharynx	92,887 (0.5)	51,005 (0.5)
Hypopharynx	80,608 (0.4)	34,984 (0.4)
Hodgkin Lymphoma	79,990 (0.4)	26,167 (0.3)
Testicals	71,105 (0.4)	9,507 (0.1)
Salivary glands	52,799 (0.3)	22,176 (0.2)
Anus	48,541 (0.3)	19,129 (0.2)

Vulva	44,235 (0.2)	15,222 (0.2)
Kaposi sarcoma	41,799 (0.2)	19,902 (0.2)
Penis	34,475 (0.2)	15,138 (0.2)
Mezotelioma	30,443 (0.2)	25,576 (0.3)
Vagina	17,600 (0.1)	8,062 (0.1)
All placements except leather	17,036,901	9,489,872
All placements	18,078,957	9,555,027

In Table 4, when both sexes are considered together (male and female), lung and breast cancers are seen more than two million times, while the number of colorectal, prostate, and gastric cancers exceeds one million, respectively, and these five cancer types constitute 46.2% of all cancers. In cancer deaths, lung cancer deaths take the first place with 1,761,007 cases and constitute 18.4% of all cancer deaths. Lung, colorectal, stomach, liver, and breast cancers take the first five places in deaths, and deaths from these cancers constitute 50.6 of all cancer deaths (Table 5). Figures 2 and 3 show the number of cancer cases and deaths in men and women in the world in 2018.

Table 4. 10 common cancer types seen most in both genders in the world, IARC, 2018

Cancer	number	%
Lung	2,093,876	11.6
Breast	2,088,849	11.6
Colorectal	1,849,518	10.2
Prostate	1,276,106	7.1
Stomach	1,033,701	5.7
Liver	841.080	4.7
Esophagus	572.034	3.2
Cervix uteri	569.847	3.2
Thyroid	567.233	3.1
Bladder	549.393	3.0
Other	6,637,320	36.6
Total	18,078,957	100

Table 5. 10 common cancer types cause of death among men in the world, IARC, 2018

Cancer	number	%
Lung	1,761,007	18.4
Colorectal	880.792	9.2
Stomach	782.685	8.2
Liver	781.631	8.2
Breast	626.679	6.6
Esophagus	508.585	5.3
Pancreas	432.242	4.5
Prostate	358.989	3.8.
Cervix uteri	311.365	3.3
Leukemia	309.006	3.2
Other	2,802,046	29.3
Total	9,555,027	100

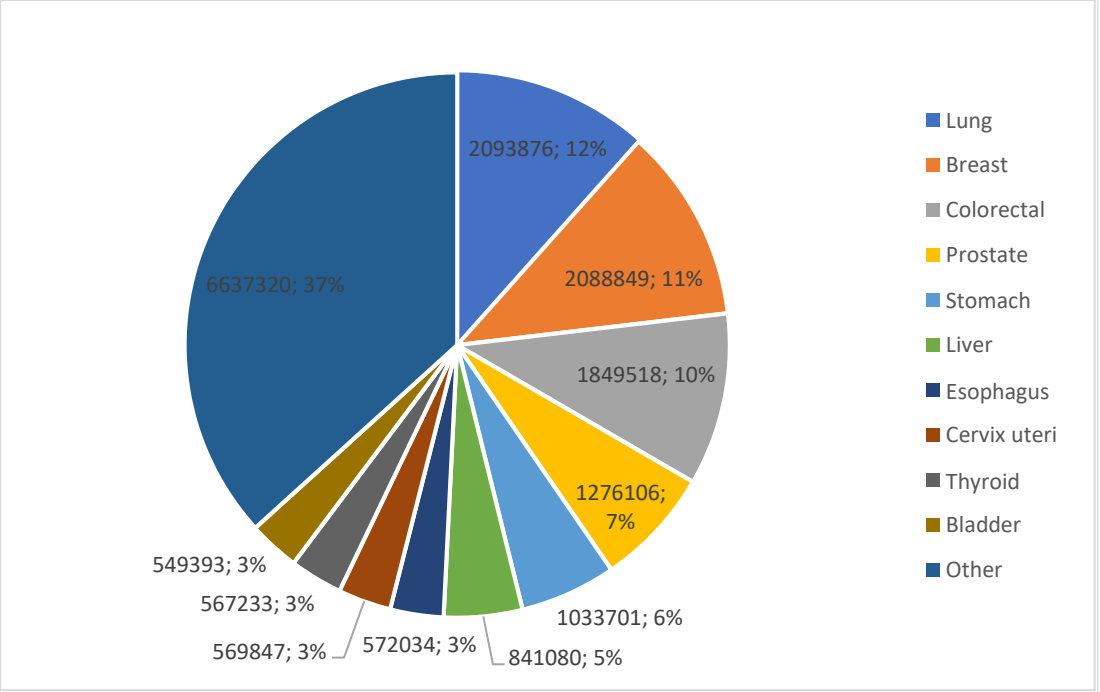


Figure 2. Number of Cases in Men and Women in 2018 in Turkey, 2018, IARC

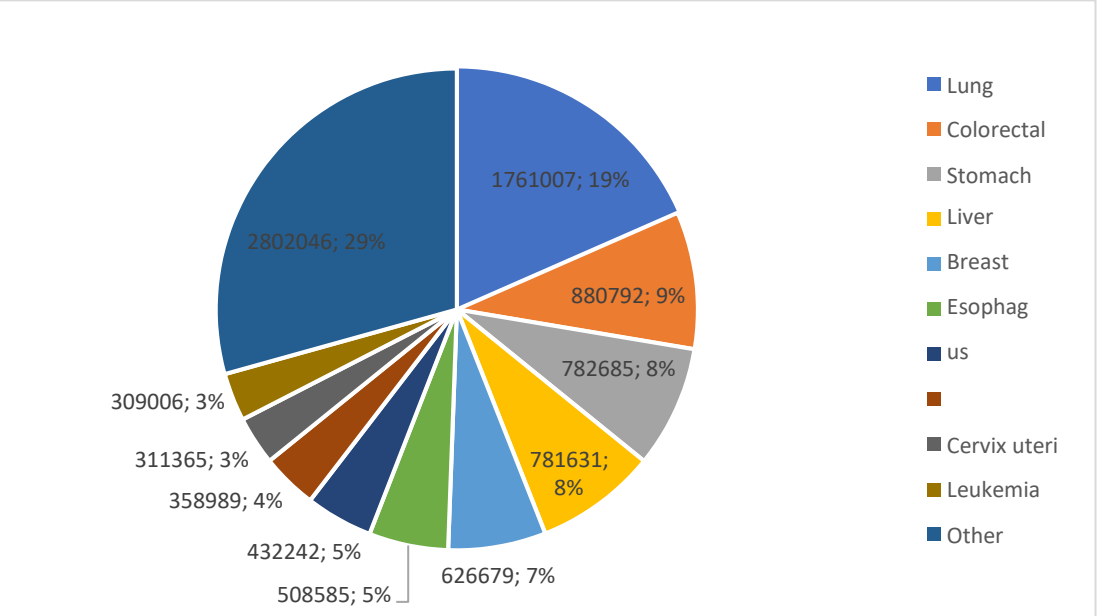


Figure 3. Cancer Deaths in Men and Women in 2018 in World, 2018, IARC

When the distribution of cancer in men is examined, lung, prostate, and colorectal cancers share the first three places with numbers exceeding one million, while stomach and liver cancers follow with figures exceeding 500 thousand. These five types of cancer

constitute 52.4% of all cancers in men. In male deaths, lung cancer-related deaths take the first place with 1,184,947, followed by liver, stomach, colorectal, and prostate cancers, and these five cancer types constitute 57.4% of deaths in men. **(Tables 6 and 7; Figures 4 and 5)**

Table 6. 10 Cancer Types most common among men in the World, IARC, 2018

Cancer	**number**	**%**
Lung	1,368,524	14.5
Prostate	1,276,106	13.5
Colorectal	1,026,215	10.9
Stomach	683.754	7.2
Liver	596.574	6.3
Bladder	424.082	4.5
Esophagus	399.699	4.2
NHL	284.713	3.0
Kidney	254.507	2.7
Leukemia	249.454	2.6
Other	2,892,790	30.6
Total	9,456,418	100

Table 7. 10 Cancer Types most common cause of death among men in the world, IARC, 2018

Cancer	**number**	**%**
Lung	1,184,947	22
Liver	548.375	10.2
Stomach	513.555	9.5
Colorectal	484.224	9.0
Prostate	358.989	6.7
Esophagus	357.190	6.6
Pancreas	226.910	4.2
Leukemia	179.518	3.3
Bladder	148.270	2.8
NHL	145.969	2.7
Other	1,237,693	23
Total	5,385,640	100

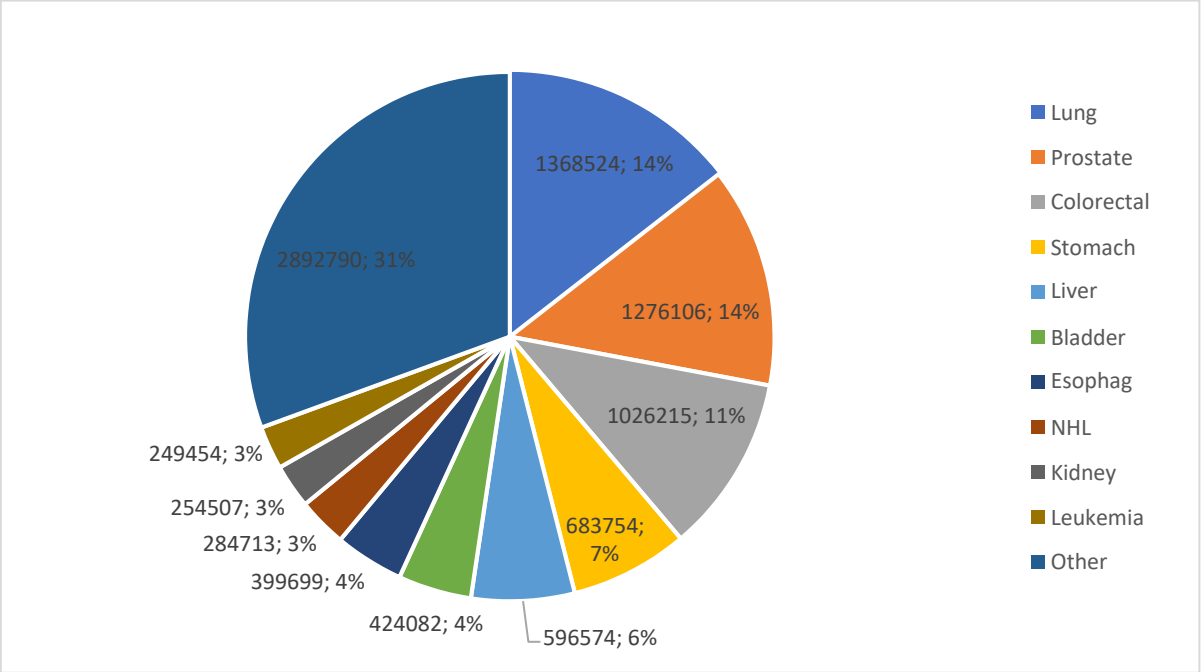


Figure 4. Number of Cases in Males in 2018 in the World, 2018, IARC

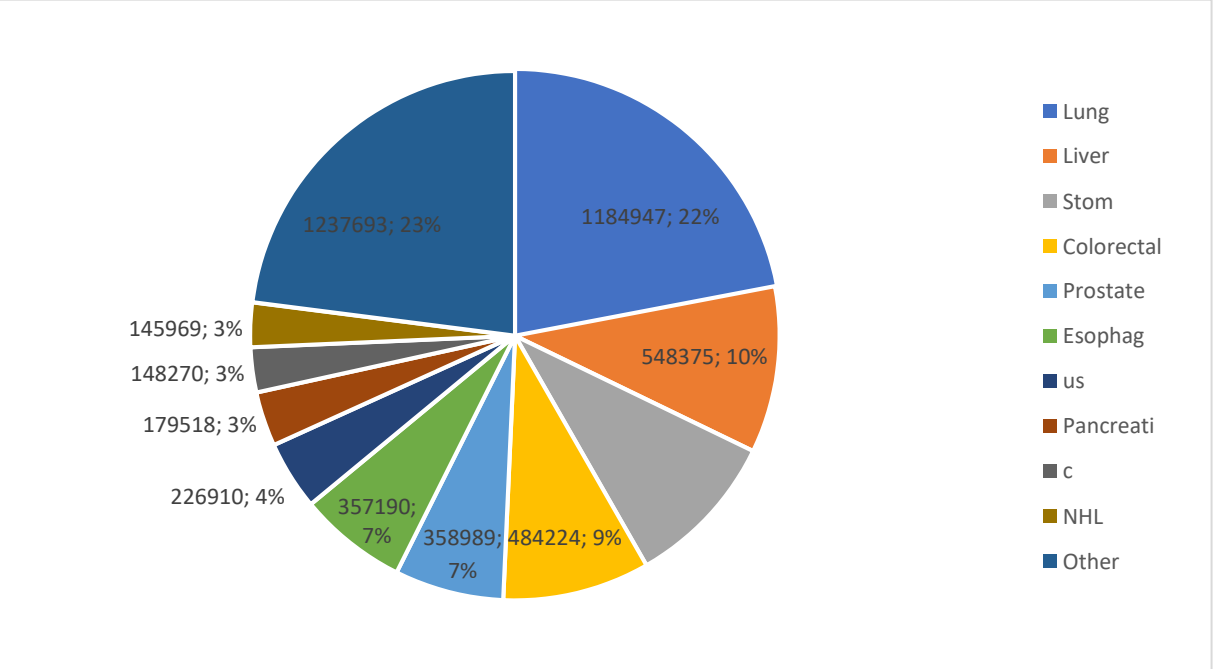


Figure 5. Cancer Deaths in Males in 2018 in the World, 2018, IARC

Among the most common cancers in women, breast cancer ranks first with more than two million, followed by colorectal, lung, and uterine cervical cancers with numbers exceeding 500 thousand, and thyroid cancer with 436,000. These five types of cancer

constitute 53,8% of cancers in women. In female cancer deaths, breast and lung cancers exceed 500 thousand, followed by colorectal, uterine cervix and gastric cancers. These five cancer types constitute 52.4% of deaths in female cancers **(**Tables 8 and 9; Figures 6 and 7)

Table 8. 10 common cancer types seen most among women in the world, IARC, 2018

Cancer	**number**	**%**
Breast	2,088,849	24.2
Colorectal	823.303	9.5
Lung	725.352	8.4
Cervix uteri	569.847	6.6
Thyroid	436.344	5.1
Uterus Corpus	382.069	4.4.
Stomach	349.947	4.1
Over	295.414	3.4
Liver	244.506	2.8
NHL	224.877	2.6
Other cancer	2,482,031	28.9
Total	8,622,539	100

Table 9. 10 common cancer types cause of death among men in the world, IARC, 2018

Cancer	**number**	**%**
Breast	626.679	15
Lung	576.060	13.8
Colorectal	396.568	9.6
Cervix uteri	311.365	7.5
Stomach	269.130	6.5
Liver	233.256	5.6
Pancreas	205.332	4.9
Over	184.799	4.4.
Esophagus	151.395	3.6
Leukemia	129.488	3.1
Other cancer	1,085,315	26
Total	4,169,387	100

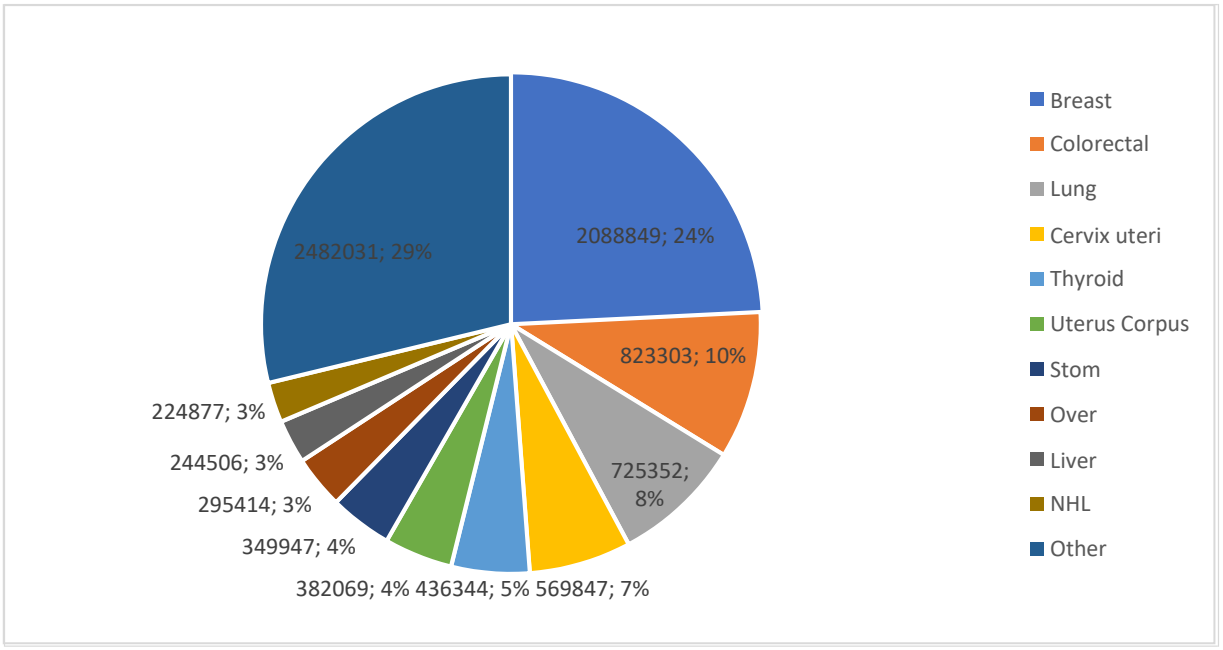


Figure 6. World, Women, 2018 Case Numbers, 2018, IARC

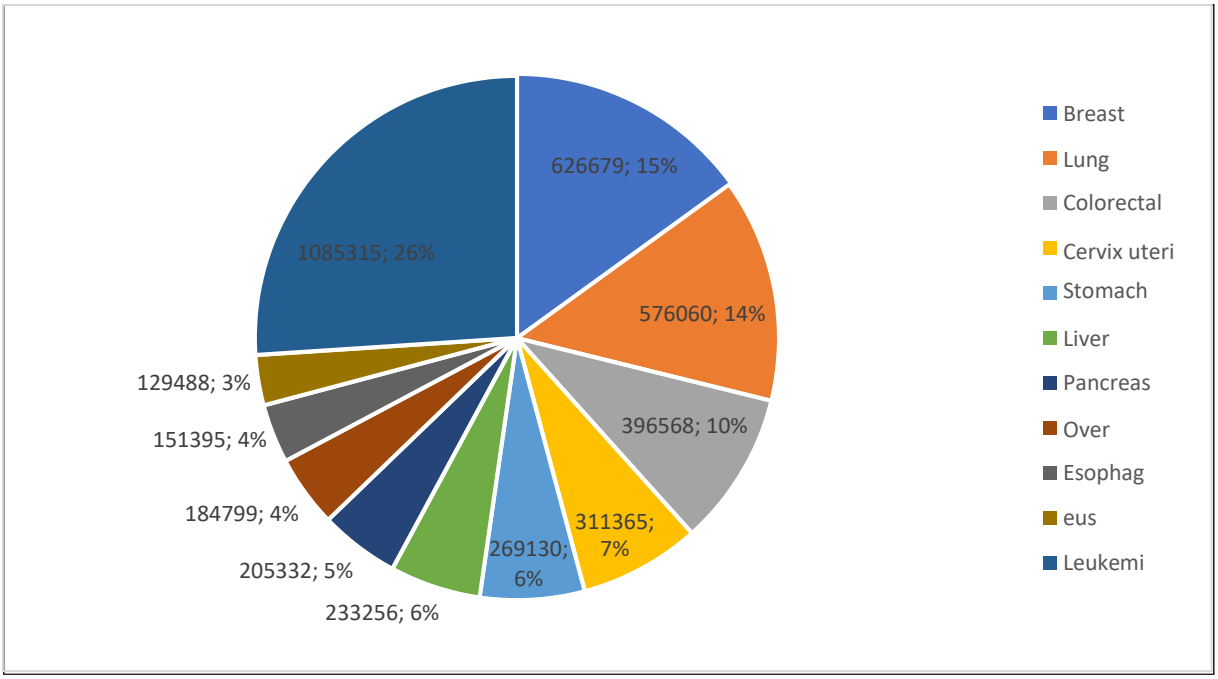


Figure 7. Cancer Deaths in Females in 2018 in the World, 2018, IARC

Cancer in Turkey

According to WHO, Globocan 2018 data, 210,537 cancer cases are seen every year and 116,710 of them die. The age-standardized cancer incidence is reported as 225.1 per hundred thousand, 284.2 in men and 182.3 in women, when both sexes are taken together.

When men and women are taken together, lung cancer is the most common cancer, which is approaching 35 thousand. Breast and colorectal cancers exceed 20 thousand, prostate cancer reaches 17 thousand, stomach and bladder cancer also exceeds 10 thousand. The first three cancers, lung, breast, colorectal, constitute 36.6% of all cancers, that is, more than one-third. When both sexes are considered together in the causes of death, lung cancer alone constitutes almost 30% of all cancer deaths with 33,683 deaths. Lung, colorectal, and gastric cancers, which make up the first three, account for almost half of all deaths, 46.1%. (Tables 10 and 11; Figures 8 and 9)

Table 10. 10 common cancer types seen both genders in Turkey, Globocan, 2018

Cancer	number	%
Lung	34.703	16.5
Breast	22.345	10.6
Colorectal	20.031	9.5
Prostate	17.332	8.2
Thyroid	13.033	6.2
Stomach	11.934	5.7
Bladder	11.235	5.3
Pancreas	6.473	3.1
Leukemia	6.029	2.9
Brain, CNS	5.909	2.8
Other cancer	61.513	29.2
Total	210.537	100

Table 11. 10 common cancer types Cause of death in both women and men in Turkey, Globocan, 2018

Cancer	number	%
Lung	33.683	28.9
Colorectal	10.033	8.6
Stomach	10.006	8.6
Pancreas	6.416	5.5
Breast	5.452	4.7
Prostate	5.165	4.4.
Brain, CNS	5.084	4.4.
Leukemia	4.681	4.0
Liver	4.307	3.7.
Bladder	4.222	3.6
Other cancer	27.661	23.7
Total	116.710	100

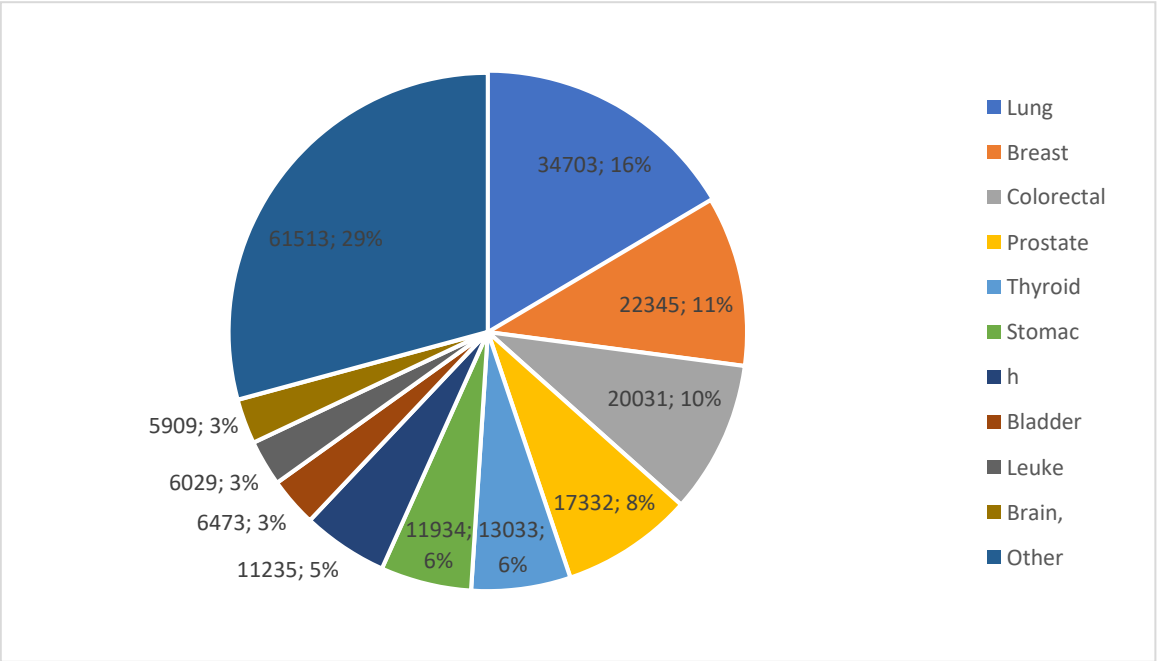


Figure 8. Number of Cases in Both Gender in 2018 in Turkey, 2018, IARC

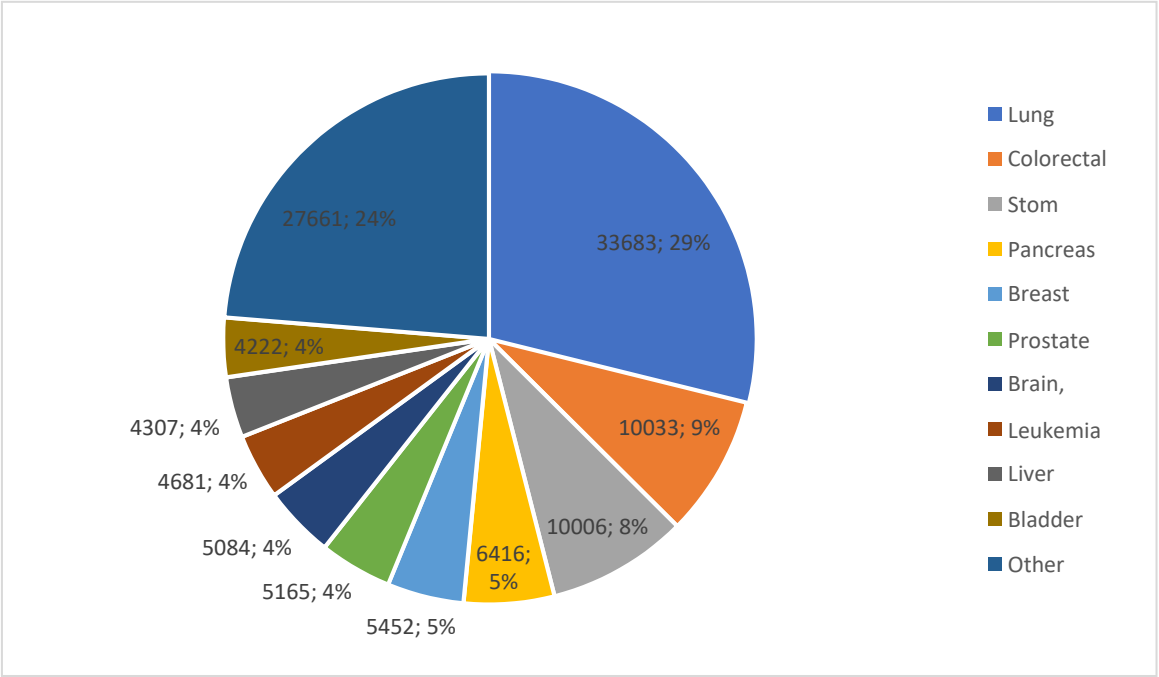


Figure 9. Cancer Deaths in Both Gender in 2018 in Turkey, 2018, IARC

When the most common cancers in men are examined, lung, prostate, colorectal bladder and gastric cancers take the first five places in the WHO, Globocan 2018 data, and these five cancer types constitute 63.3% of all cancers in men. Undoubtedly, lung cancer is very advanced in Turkey. One-fourth of all cancers in men are lung cancer, and nearly 30 thousand cases of lung cancer are seen.

When we look at deaths, lung, stomach, colorectal, prostate and pancreatic cancers take the first five places in men. These top five causes constitute 66.2% of all deaths. Lung cancer alone accounts for 38.3% of all cancer deaths in men. (Tables 12 and 13, Figures 10 and 11)

Table 12. The most common cancers seen most among men in the world, Globocan, 2018

Cancer	**number**	**%**
Lung	29.405	24.7
Prostate	17.332	14.6
Colorectal	11.548	9.7
Bladder	9.578	8.1
Stomach	7.414	6.2
Pancreas	3.633	3.1
Larynx	3.532	3.0
Leukemia	3.385	2.8
Brain, CNS	3.181	2.7
NHL	3.100	2.6
Other cancer	26.774	22.5
Total	118.882	100

Table 13. The most common cancers cause of death among men Turkey, Globocan, 2018

Cancer	**number**	**%**
Lung	28.525	38.3
Stomach	6.376	8.6
Colorectal	5.571	7.5
Prostate	5.165	6.8
Pancreas	3.622	4.9
Bladder	3.532	4.7
Brain, CNS	2.837	3.8.
Liver	2.747	3.7.
Leukemia	2.676	3.6
Larynx	1.660	2.2.
Other cancer	11.831	15.9
Total	74.542	100

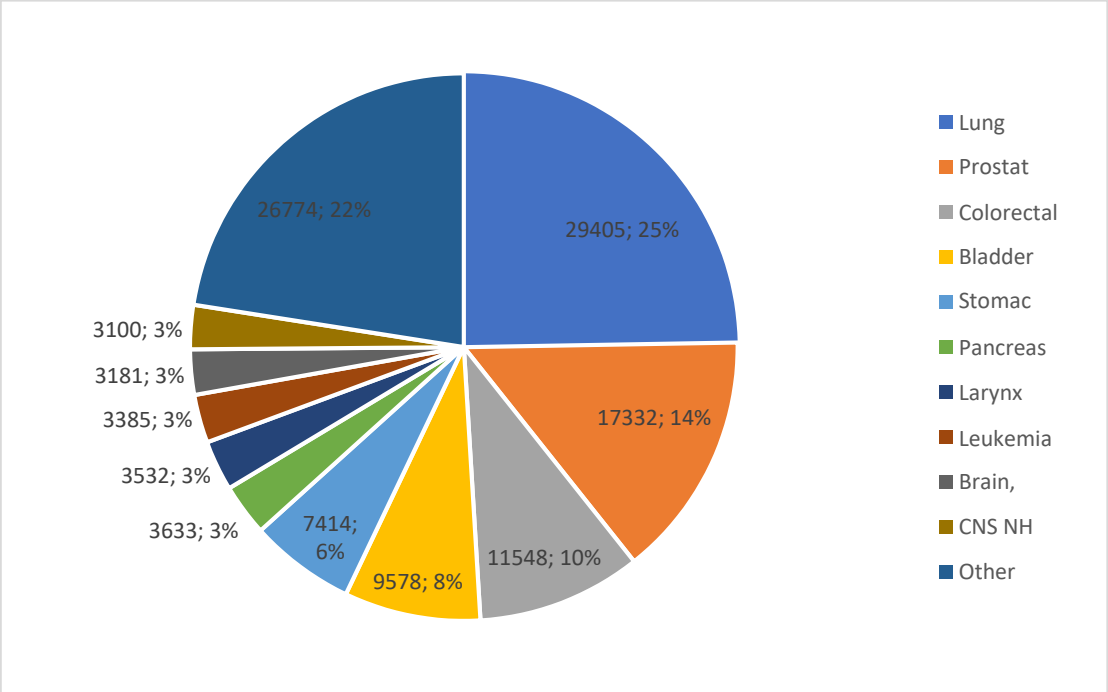


Figure 10. Number of Cases in Males in 2018 in the World, 2018, IARC

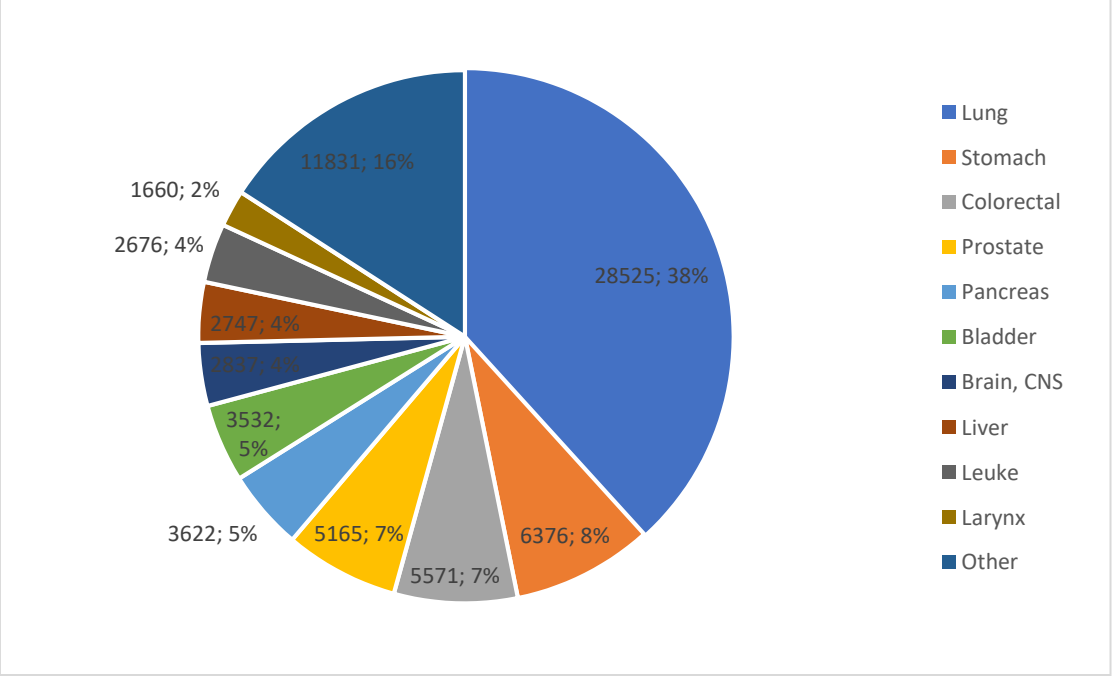


Figure 11. Cancer Deaths in Males in 2018 in Turkey, 2018, IARC

Breast cancer ranks first with 22,435 cases in WHO, Globocan 2018 data in female cancers, followed by the thyroid, colorectal, uterine corpus, and lung cancers. These five cancer types constitute 56.9% of all female cancers. The five leading causes of death in female cancers are breast, lung, colorectal, stomach, and pancreatic cancers, and these five cancer types account for 51% of all deaths. (Tables 14 and 15, Figures 12 and 13)

Table 14. 10 common cancer types seen most among women in the world, Globocan, 2018

Cancer	**number**	**%**
Breast	22.435	24.5
Thyroid	10.563	11.5
Colorectal	8.483	9.2
Corpusuteri	5.463	6.0
Lung	5.298	5.8
Stomach	4.520	4.9
Over	3.729	4.1
Pancreas	2.840	3.1
Brain, CNS	2.728	3.0
Leukemia	2.644	2.8
Other cancer	23.042	25.1
Total	91.745	100

Table 15. 10 common cancer types cause of death among women in Turkey, Globocan, 2018

Cancer	**number**	**%**
Breast	5.452	12.9
Lung	5.158	12.2.
Colorectal	4.462	10.6
Stomach	3.630	8.7
Pancreas	2.794	6.6
Brain, CNS	2.247	5.3
Over	2.191	5.2
Leukemia	2.005	4.8
Liver	1.560	3.7.
Cervix uteri	1.280	3.0
Other cancer	11.389	27.0
Total	42.168	100

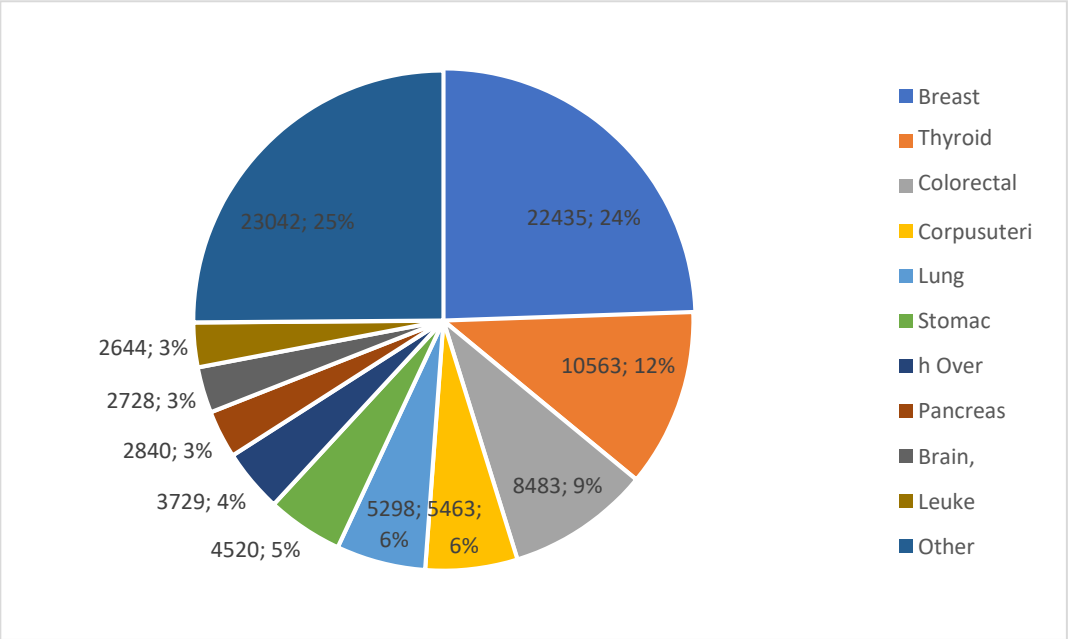


Figure 12. **Turkey, Women, 2018 Case Numbers, 2018, IARC**

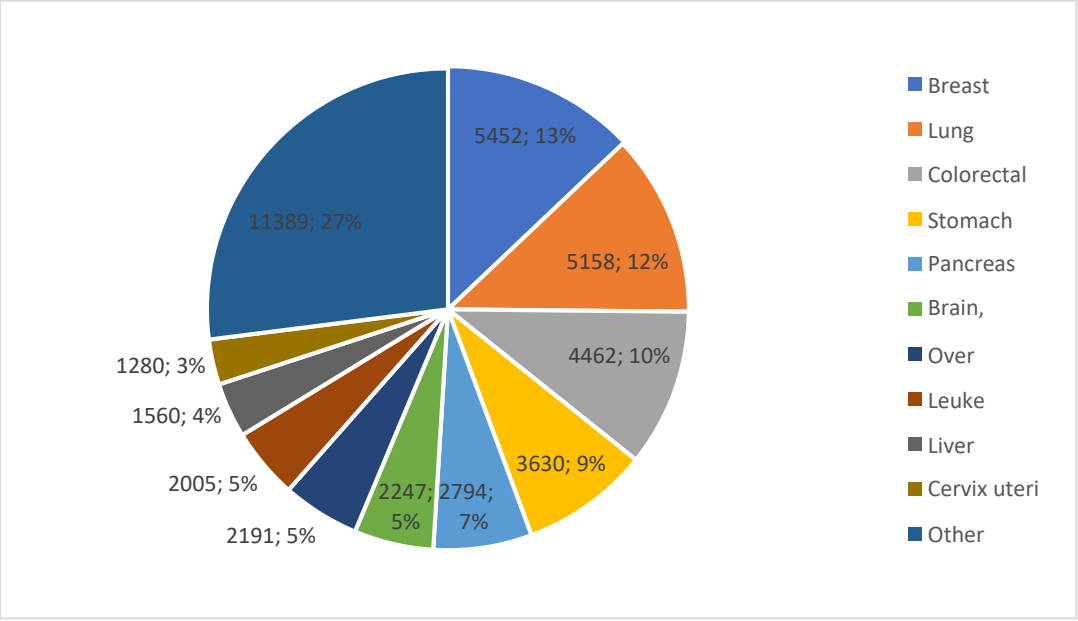


Figure 13. Cancer Deaths in Females in 2018 in Turkey, 2018, IARC

Cancer statistics in Turkey are prepared from the data of 14 provinces, which are accepted in terms of quality and completeness, obtained through the cancer registry. The population of Turkey in 2017 is 80,810,525. The age-standardized incidence of cancer has been reported as 259.2 per hundred thousand in men and

187.0 per hundred thousand in women. (Figure 14) According to 2017 cancer statistics, it is estimated that there are 180,288 cancer cases in Turkey.

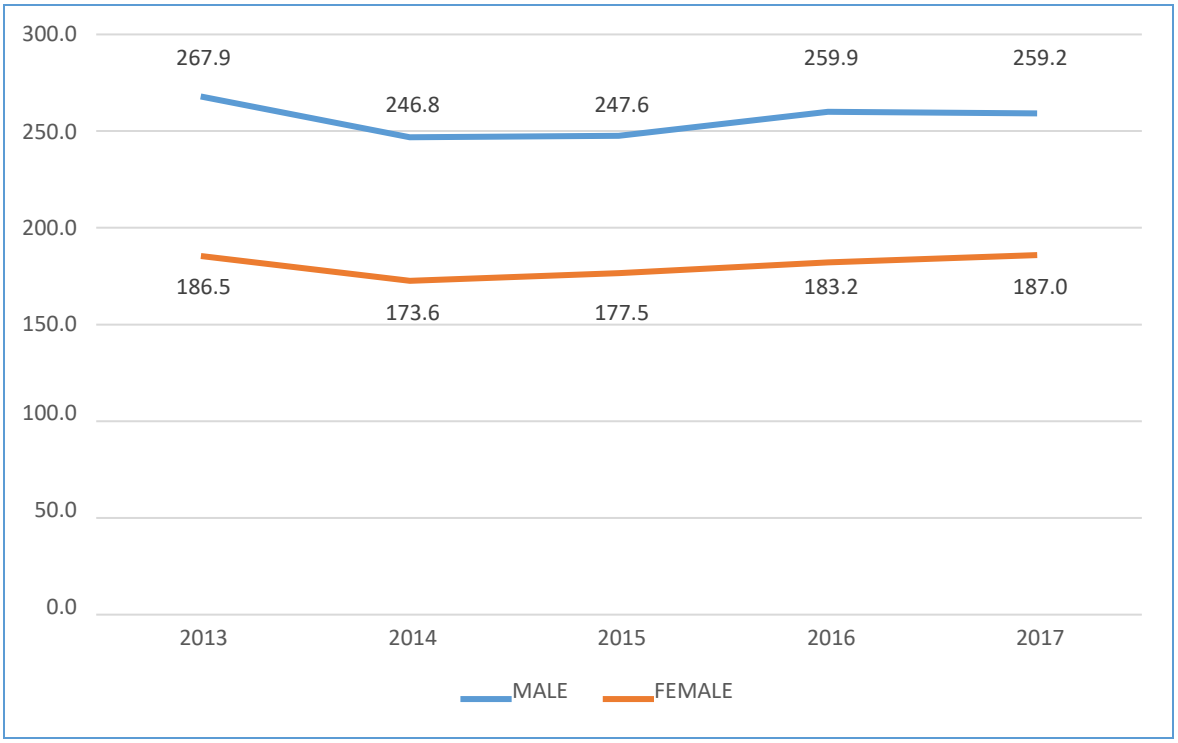


Figure 14. Distribution of Age Standardized Incidence Rates for All Cancers According to Gender Between 2013 and 2017 (Turkey Compositional Data Base, 2013-2017) (World Standard Population, per 100,000 individuals)

T.R. According to the data of the Ministry of Health, when the age-standardized incidence rates of 10 cancers that are common in men and women are examined, it is estimated that lung, prostate, colorectal, bladder, and gastric cancers are the most common cancers in men, constituting 58.2% of all cancers in men. In women, breast, thyroid, colorectal, trachea/bronchus/lung, uterine corpus cancers are the most common cancers and are estimated to constitute 57.1% of all female cancers. (Figure 15,16,17,18)

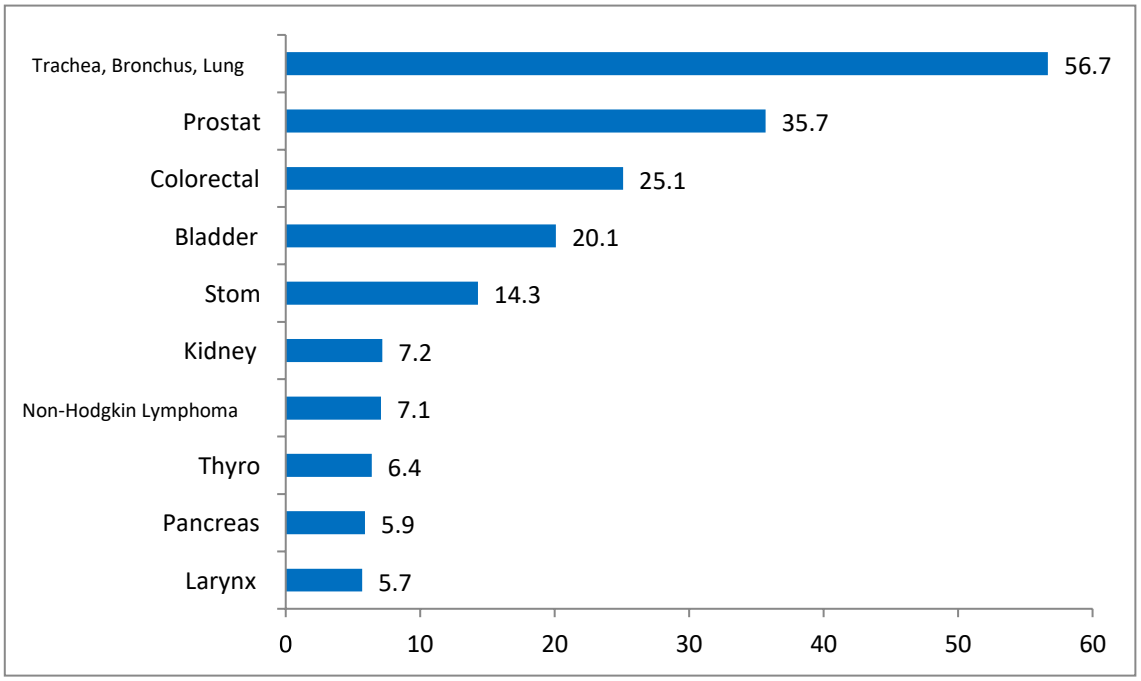


Figure 15. Age-Standardized Rates of 10 Cancer Types Which Are Most Common in Males (Turkey Compositional database, 2017) (World Standard Population, per 100,000 individuals)

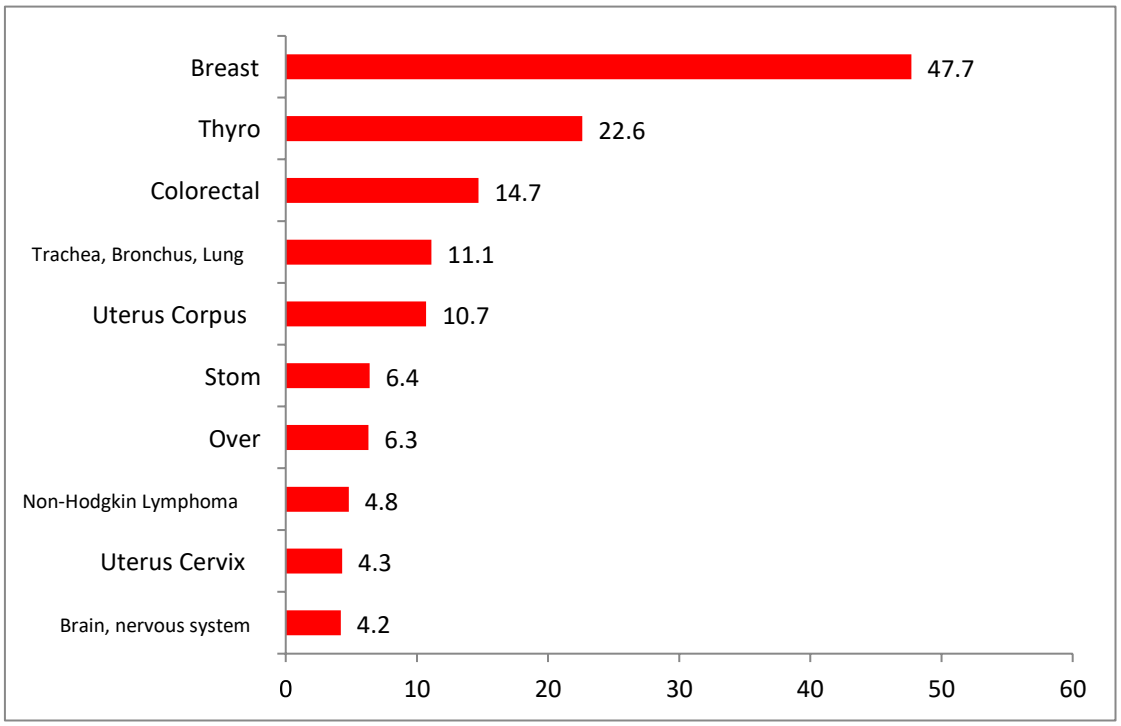


Figure 16. Age-Standardized Rates of 10 Cancer Types Which Are Most Common in Females (Turkey Compositional database, 2017) (World Standard Population, per 100,000 individuals)

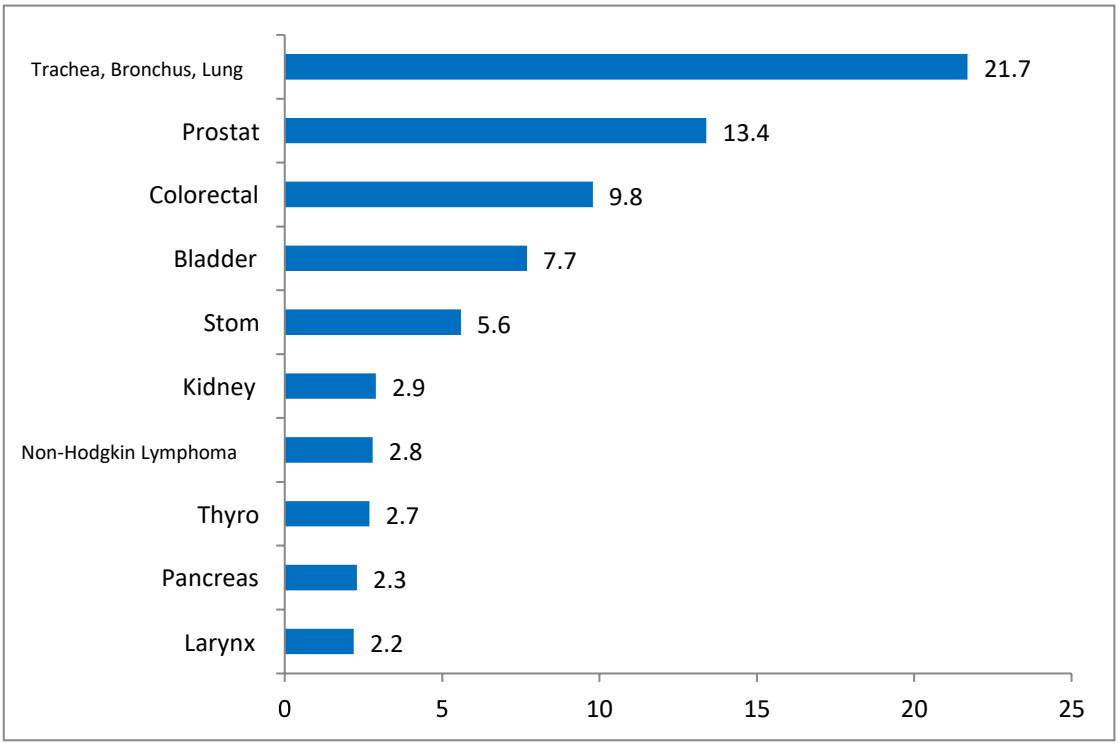


Figure 17. Percentage Distribution of Some Most Common Cancers in Males of All Age Groups Within This Group(Turkey Compositional Data Base, 2017)

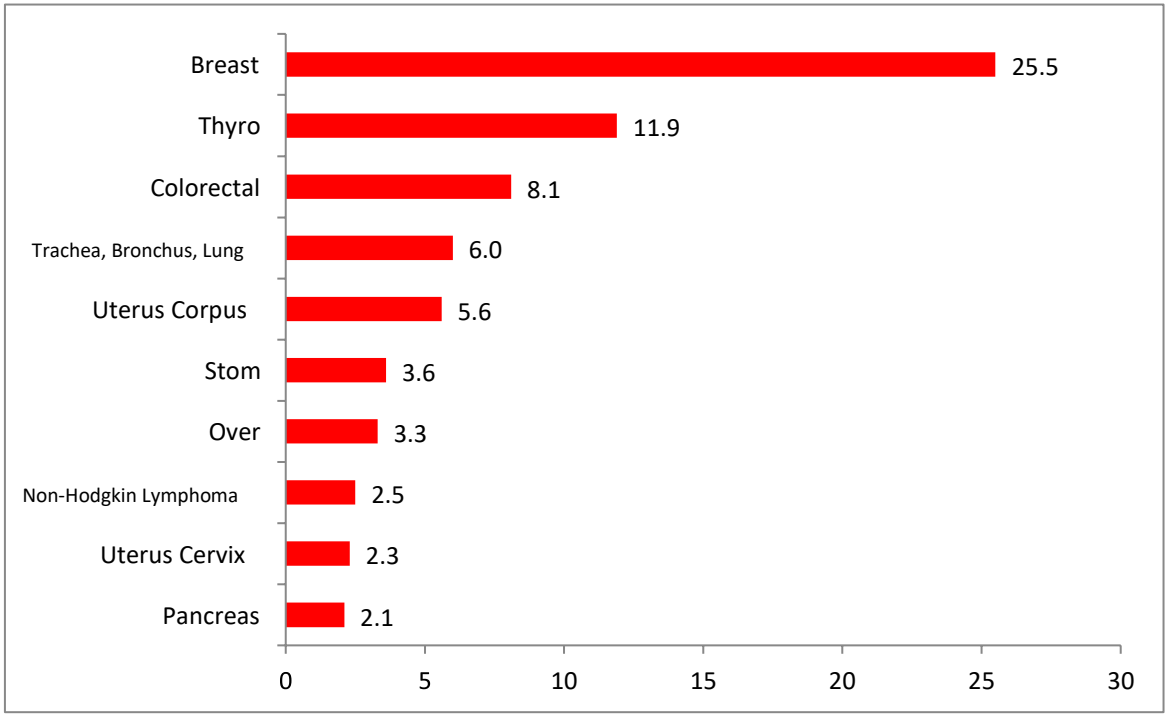


Figure 18. Percentage Distribution of Some Most Common Cancers in Females of All Age Groups Within This Group (Turkey Compositional Data Base, 2017)

RESOURCES

1. Bernard W. Stewart and Christopher P. Wild (eds) World Cancer Report 2014, WHO Press, Geneva, 2014
2. GLOBOCAN 2018, Global Cancer Observatory http://gco.iarc.fr/ International Agency for Research on Cancer 2020 (Access date: 20 June 2020)
3. Bray F, Ferlay J, Soerjomataram I, Siegel, RL, Torre LA, Jemal A. Global Cancer Statistics 2018: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA: Cancer J Clin. 2018; 68:394-424.
4. Kara F, Keskinkılıç B (Eds) Türkiye Kanser İstatistikleri, 2017. Ministry of Health, 2021
5. Death Reason Statistics, Turkey Statistics Institute, 2017. http://www.tuik.gov.tr/PreHaberBultenleri.do?id=27620&utm_source=feedburner&utm_medium=feed&utm_campaign=Feed%3A+tuikbulten+%28TÜİK-Haber+Bültenleri+%28Son+1+Ay%29%29 (Access Date 20 June 2020)
6. Atun R, Bhakta N, Avram Denburg A, et al. The Lancet Oncology Commission Sustainable care for children with cancer: a Lancet Oncology Commission Lancet Oncol 2020 21: e185-e224,2020
7. Kutluk MT, Yeşilipek A. Pediatric cancer registry in Turkey 2009-2019 (TPOG & TPHD). ASCO 2020 Annual meeting. J Clin Oncol 38: 2020 (suppl; abstr e22513) DOI: 10.1200/JCO.2020.38.15_suppl.e22513

SECTION 8

CANCER ACTION PLANS

Strategy	Activities	Institution(s) in Charge	Institution(s) to cooperate	Completion Date	Possible Obstacles	Progress Indicators	Monitoring and Control Data
Turkey Asbestos Control Strategic Plan	• *PHASE I has been completed. • PHASE II: It is under the responsibility of the Ministry of Environment and Urbanization.	• Ministry of Environment and Urbanization		• December 2023			

*Within the scope of Phase I studies carried out under the responsibility of HSGM (THSK): Asbestos situation analysis was made and the provinces where the program would be carried out were determined. The training given to the Public Health Managers regarding the program has been completed. Data on diseases caused by asbestos exposure from provinces were collected and analyzed. Community leaders were trained to inform the public about the issue. Brochures, posters, and booklets were prepared and distributed for public awareness. Samples were taken from households in areas where asbestos exposure was detected and analyzed.

Strategy	Activities	Institution(s) in Charge	Institution(s) to cooperate	Completion Date	Possible Obstacles	Progress Indicators	Monitoring and Control Data
˚**Turkey Radon Mapping and National Radon Control Program**˚	• * The first phase of the program has been completed. • In the provinces where radon measurement is made, the analysis phase of the "Radon Research Questionnaire at Homes" applied to the households simultaneously during the first phase will be completed and reported. • It is planned to raise awareness about radon throughout the society, primarily in households with high measurement values, and to initiate rehabilitation studies where necessary.	• Chairman of GDPH Cancer Department • TAEK	• GDPH Departments • Provincial Health Directorates • Universities • TAEK	• December 2023	• Insufficient public participation in education	• Number of people trained	• Planning and implementation of questionnaires to evaluate awareness as a result of training given to the public.

˚In the first phase of the program, it was aimed to create a "Turkey Radon Map" by conducting a due diligence study covering 81 provinces, and then to develop a "National Radon Control Program". Studies carried out within the scope of the creation of the "Radon Map of Turkey", which is the first stage of the program: Training of the personnel who will run the program in the provinces was carried out. The sample to represent Turkey on a household basis

was determined in consultation with TurkStat. Radon measurement detectors were placed in the detected households. The inserted detectors were collected after 2 months. Analysis of the detectors was carried out in TAEK laboratories.

Strategy	Activities	Institution(s) in Charge	Institution(s) to cooperate	Completion Date	Possible Obstacles	Progress Indicators	Tracking and Control Data
Ensuring the functionality of cancer registry centers established in 81 provinces	• Evaluating cancer registry centers in Provincial Health Directorates on site • To train cancer registry staff	• GDPH Departments • Provincial Health Directorates	• MoH Health Information Systems GM • GDPH Departments • University Hospitals • Private Hospitals and health institutions • WHO-IARC	• December 2023	• Lack of staff • Intense staff circulation • Assignment of certified personnel to other fields • Infrastructure issues • Insufficient awareness of managers about cancer registry	• Number of basic cancer registry modules training conducted • Number of personnel receiving certified training / Number of certified personnel working in the field • Compliance and acceptance of collected data with IARC data standards • Ensuring data flow with public institutions and organizations in appropriate standards	• Analysis of the current situation • Number of certified personnel • Number of people who attended the trainings • Data from all organizations

Strategy	Activities	Institution(s) in Charge	Institution(s) to cooperate	Completion Date	Possible Obstacles	Progress Indicators	Monitoring and Control Data
Improving cancer registry data quality	• Raising awareness in cancer registry staff • To check the completeness of cancer records • Checking for inconsistencies in records • Supply of educational materials	• GDPH Departments • Provincial Health Directorates	• MoH Health Information Systems GM • GDPH Departments • Private Hospitals • WHO-IARC	• December 2023	• Increasing burden of cancer disease in society • Insufficient number of certified personnel who can work in quality and completeness control	• Number of provinces from which data used in Turkey Cancer Statistics come from • Number of cancer registry centers included in IARC's book "Cancer Incidence in Five Continents" and the CONCORDE study investigating Global Cancer Survival • Cancer data quality of provinces • Percentages of completeness, validity, and timeliness of annual cancer data in Turkey	• Analysis of the current situation • HSGM Monitoring, Evaluation and Statistics Department and Cancer Department monitoring and evaluation reports • Number of provinces from which data used in Turkey Cancer Statistics come from • Increase in the number of cancer registry centers in our country that take part in IARC's Cancer Incidence Book and CONCORDE Survival Study in Five Continents

Strategy	Activities	Institution(s) in Charge	Institution(s) to cooperate	Completion Date	Possible Obstacles	Progress Indicators	Monitoring and Control Data
Improvement and increasing the coverage of breast, cervical and colorectal cancer screening	• Ensuring the active participation of Family Medicine in cancer screenings • Increasing the device, equipment and technical service quality of the centers to be scanned • Increasing the number of scanning centers • Increasing the number of mobile scanning vehicles • Organizing awareness and education campaigns for citizens to participate in screenings	• HSGM Head of Department of Cancer	• Departments related to HSGM • MoH Health Information Systems GM • MoH Health Promotion GM • Provincial Health Directorates • Public, Private, Foundation and University Hospitals • NGOs • SSI • Related Ministries • WHO-IARC	• December 2023	• Lack of staff and motivation in Family Health Centers • Insufficient awareness and education level of the people • Reluctance of citizens to participate in screenings • Insufficient coordination between the cooperating institutions • Lack of trained personnel • Provincial administrators do not give due importance to the issue	• Increasing the number of people participating in screening programs every year	• The increasing rate of cancer detected in early-stage • Expected and actual cancer death rates