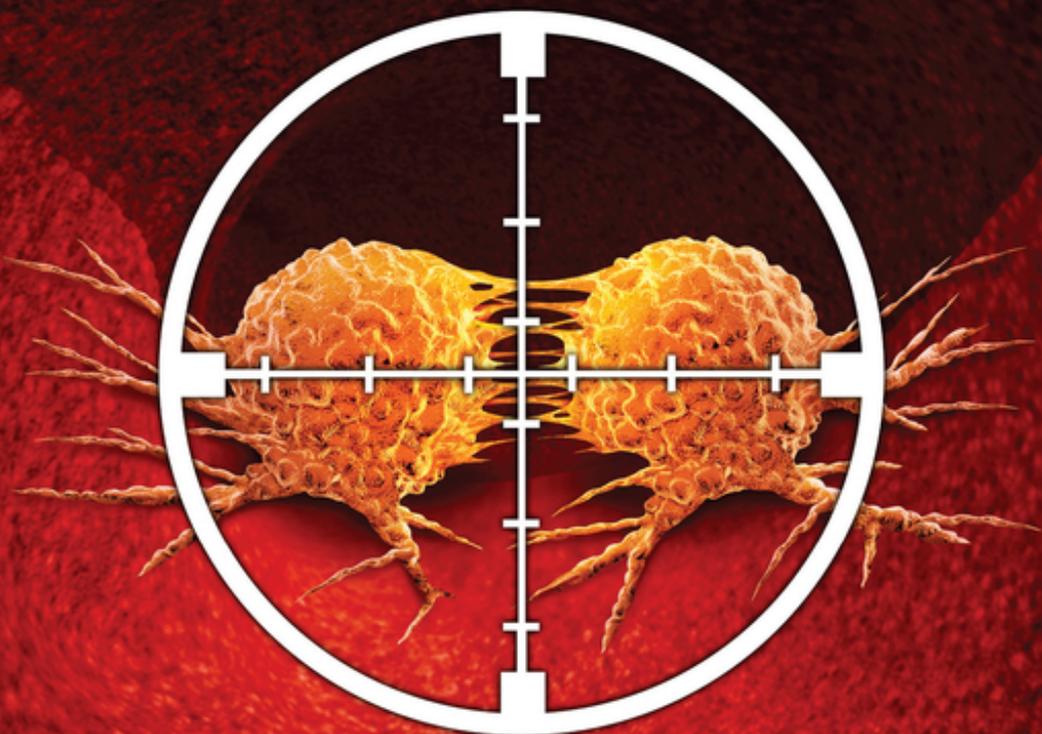


Surya K. De

Fundamentals of Cancer Detection, Treatment, and Prevention



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Surya K. De

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Author

Dr. Surya K. De

Conju-Probe
San Diego
CA
United States

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- There may be underlying medical problems requiring detection by a physician.

*Dedicated to my Parents:
Late (Mrs.) Putibala De
Late (Mr.) Jatindra Nath De*

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Preface

Cancer is the second leading cause of death worldwide, with nearly 1 in 6 mortalities per year attributed to various forms of this illness. Understanding cancer is not simple, as it is a complex and constantly evolving cellular disease.

My aim in this book is to educate readers about the basics of cancer – from its causes, symptoms, and diagnosis to the variety of available treatment options. Having a clearer comprehension of the condition is vital for undertaking steps to prevent it, and for those already diagnosed, choosing the appropriate and most curative therapy.

Whether read by a medical student, scientist, doctor, or layperson, this book is a handy, basic reference and interesting compendium of information about a disease that is unfortunately so widespread; it is relevant to everyone.

I am deeply grateful to my family for their consistent understanding and support throughout the completion of this project.

As always, I welcome and, in fact, earnestly request readers to notify me of any suggestions for improving this book. Please send your comments to this email: desurya125@gmail.com

2021, San Diego
California, United States

Surya K. De, PhD, FRSC, CChem.

About the Book

Cancer is the second leading cause of death worldwide, with its various forms resulting in nearly one out of every six mortalities each year. Because cancer is a complex and constantly evolving cellular disease, understanding it may seem difficult. This book, however, provides a comprehensive overview of human cancer that can be easily grasped by medical students, doctors, scientists, and laypeople alike. Explore the basics of this disease – from its causes, symptoms, and diagnosis to the variety of treatment options available – all expressed in clear, simple language and through informative illustrations. Knowledge is the best way to eliminate the mystery and fear surrounding the disease of cancer. Through this book, readers are given the power to make lifestyle adjustments to avoid the illness and stay healthy, or if already diagnosed, hope in the realization that curative therapies are available and constantly being improved through ongoing research. All FDA-approved drugs including small molecules, peptides, monoclonal antibody, whole antibody, gene therapy, antibody–drug conjugation, cell therapy, and others are included with drug names and brand names, medical uses, and targets.

About the Author

Dr. Surya K. De was born in a village (Takrar) near the Indian Institute of Technology, Kharagpur, West Bengal, India, completing a university-level education in his home country prior to being encouraged by his parents to pursue postgraduate training in the United States. After extensive postdoctoral studies and research appointments at the University of Washington, Purdue University, and the world-renowned Scripps Research Institute, he worked at Sanford Burnham Prebys Medical Discovery Institute in La Jolla, California, prior to his current role at another major biotechnological firm in San Diego as an expert in small-molecule-based pharmaceutical research. Dr. De has published over 100 papers in reputed international journals, covering a broad array of specialized topics in science, and he holds fifteen United States' and international patents. Due to his abundant research contributions in the areas of cancer, metabolic diseases, organic and medicinal chemistry, and neuroscience, Dr. De earned the distinction of Fellow of the Royal Society of Chemistry in 2010, and was subsequently awarded the status of Chartered Chemist in 2011. In addition, he is an elected Councilor in the San Diego Section of the American Chemical Society. Dr. De resides in San Diego, California, where he loves the scenic coastline and sunny skies.

San Diego, California, United States

Surya K. De, PhD, FRSC, CChem

Common Abbreviations and Acronyms

5-FU:	5-fluorouracil
6-MP:	6-mercaptopurine
6-TG:	6-thioguanine
AA:	Anaplastic anemia
ABC:	Advanced breast cancer
ACE:	Angiotensin-converting enzyme
ABMT:	Autologous bone marrow transplant
ADR:	Adverse drug reaction
ADP:	Adenosine diphosphate
AFP:	Alpha-fetoprotein
AIDS:	Acquired immunodeficiency syndrome
ALAT:	Alanine aminotransferase
ALCL:	Anaplastic large-cell lymphoma
ALK:	Anaplastic lymphoma kinase
AML:	Acute myeloid leukemia
ALL:	Acute lymphoblastic leukemia
ALT:	Alanine aminotransferase
AMKL:	Acute megakaryocytic leukemia
AMP:	Adenosine monophosphate
ATP:	Adenosine triphosphate
BCC:	Basal cell carcinoma
BPDCN:	Blastic plasmacytoid dendritic cell neoplasm
Bcl2:	B-cell lymphoma 2
BMI:	Body mass index
BTK:	Bruton's tyrosine kinase
<i>BRCA1</i> :	Breast cancer gene 1
<i>BRCA2</i> :	Breast cancer gene-2
CA-125:	Cancer antigen 125
CAT:	Computerized axial tomography
CAR-T:	Chimeric antigen receptor T cells
CBC:	Complete blood count
CDC:	Centers for Disease Control and Prevention
CDK:	Cyclin-dependent kinase

CT:	Computed tomography
CLL:	Chronic lymphocytic leukemia
CTCL:	Cutaneous T-cell lymphoma
CTLA-4:	Cytotoxic T-lymphocyte-associated antigen-4
CML:	Chronic myelogenous leukemia
CAT:	Computerized axial tomography (scan)
CMML:	Chronic myelomonocytic leukemia
CNS:	Central nervous system
CHF:	Congestive heart failure
COPD:	Chronic obstructive pulmonary disease
CPK:	Creatine phosphokinase
CPR:	Cardiopulmonary resuscitation
CRF:	Chronic renal failure
CR:	Complete remission
CXR:	Chest X-ray
DM:	Diabetes mellitus
DNA:	Deoxyribonucleic acid
DLBCL:	Diffuse large B-cell lymphoma
DLCL:	Diffuse large-cell lymphoma
EBV:	Epstein-Barr virus
EGFR:	Epidermal growth factor receptor
ERK:	Extracellular signal-regulated kinase
ECG/EKG:	Electrocardiogram
ENT:	Ear, nose, and throat
FSH:	Follicle-stimulating hormone
GERD:	Gastroesophageal reflux disease
GIST:	Gastrointestinal stromal tumor
GBM:	Glioblastoma multiforme
GI:	Gastrointestinal
GFR:	Glomerular filtration rate
HAV:	Hepatitis A virus
HBV:	Hepatitis B virus
HPC:	Hepatitis C virus
HIV:	Human immunodeficiency virus
HCC:	Hepatocellular carcinoma
HCL:	Hairy cell leukemia
HL:	Hodgkin's lymphoma
HPV:	Human papillomavirus
HDL:	High-density lipoprotein
HGB:	Hemoglobin
HRT:	Hormone replacement therapy
IBD:	Inflammatory bowel disease
IBS:	Irritable bowel syndrome
ICD:	Implantable cardioverter-defibrillator
ICU:	Intensive care unit

IDDM:	Insulin-dependent diabetes mellitus
IM:	Intramuscular
IP:	Intraperitoneal
IT:	Intrathecal
IV:	Intravenous
IL-2:	Interleukin-2
IUD:	Intrauterine device
IVP:	Intravenous pyelogram
IgH:	Immunoglobulin heavy chain
iMiD:	Immunomodulatory drugs
Kg:	Kilogram
LDL:	Low-density lipoprotein
LFT:	Liver function test
LCH:	Langerhans cell histiocytosis
LDH:	Lactic dehydrogenase
LMM:	Lentigo maligna melanoma
LN:	Lymph node
LP:	Lumbar puncture
MAPK:	Mitogen-activated protein kinase
MRI:	Magnetic resonance imaging
MDS:	Myelodysplastic syndromes
MCL:	Mantle cell lymphoma
MM:	Multiple myeloma
MDR:	Multidrug-resistant
MI:	Myocardial infarction (heart attack)
MMR:	Measles, mumps, and rubella
MRI:	Magnetic resonance imaging (scan)
MRT:	Malignant rhabdoid tumor
MRSA:	Methicillin-resistant staphylococcus aureus
MS:	Multiple sclerosis
MTD:	Maximum tolerated dose
NG:	Nasogastric
NIDDM:	Non-insulin-dependent diabetes mellitus
NKDA:	No known drug allergies
NSAID:	Non-steroidal anti-inflammatory drug
NSCLC:	Non-small cell lung cancer
NHL:	Non-Hodgkin's lymphoma
NPC:	Nasopharyngeal carcinoma
NRSTS:	Non-rhabdomyosarcoma soft-tissue sarcomas
NSCLC:	Non-small cell lung cancer
OCD:	Obsessive-compulsive disorder
ORR:	Overall response rate
OS:	Overall survival
PAD:	Peripheral arterial disease
PAT:	Paroxysmal atrial tachycardia

PAP:	Papanicolau (a test for cervical cancer)
PET:	Positron emission tomography
PFT:	Pulmonary function test
PID:	Pelvic inflammatory disease
PI-3K:	Phosphoinositide 3-kinase
PMS:	Premenstrual syndrome
PPD:	Purified protein derivative
PT:	Prothrombin time
PTH:	Parathyroid hormone
PTSD:	Post-traumatic stress syndrome
PTT:	Partial thromboplastin time
PTEN:	Phosphatase and tensin homolog
PSA:	Prostate-specific antigen
PARP:	Poly (ADP ribose) polymerase
PD1:	Programmed cell death protein 1
PD-L1:	Programmed death-ligand 1
PO:	Per os (by mouth)
PUD:	Peptic ulcer disease
PVC:	Premature ventricular contraction
PFS:	Progression-free survival
PD-1:	Programmed cell death protein-1
PR:	Partial remission
RA:	Rheumatoid arthritis
RCT:	Randomized controlled trial
RNA:	Ribonucleic acid
RBC:	Red blood cell/red blood count
RSV:	Respiratory syncytial virus
RCC:	Renal cell carcinoma
RANK:	Receptor activator of nuclear factor-kappa B
RTK:	Receptor tyrosine kinase
SAD:	Seasonal affective disorder
SIDS:	Sudden infant death syndrome
SLE:	Systemic lupus erythematosus
SC:	Subcutaneous
SCC:	Squamous cell carcinoma
SCLC:	Small cell lung cancer
STD:	Sexually transmitted disease
SCNSL:	Secondary central nervous system lymphoma
TB:	Tuberculosis
TAH:	Total abdominal hysterectomy
TIA:	Transient ischemic attack (stroke)
TIBC:	Total iron-binding capacity
TCC:	Transitional cell carcinoma
TFG- β :	Transforming growth factor beta
TMJ:	Temporomandibular joint

TNF:	Tumor necrosis factor
TNBC:	Triple-negative breast cancer
TBI:	Total body irradiation
TCP:	Thrombocytopenia
TSH:	Thyroid-stimulating hormone
TURP:	Transurethral resection of prostate gland
US:	Ultrasound (scan)
URI:	Upper respiratory infection
UTI:	Urinary tract infection
UVR:	Ultraviolet radiation
VEF:	Ventricular ejection fraction
VEGFR:	Vascular endothelial growth factor receptor
VHL:	Von Hippel-Lindau
WBC:	White blood cell count
WCC:	White cell count
WM:	Waldenstrom's macroglobulinemia
XRT:	Radiotherapy (external)
YST:	Yolk sac tumor

List of Acronyms of Cancer Organizations

AACR:	American Association for Cancer Research
ABPI:	Association of the British Pharmaceutical Industry
ABTA:	American Brain Tumor Association
ACDM:	Association for Clinical Data Management
ACRPI:	Association of Clinical Research for the Pharmaceutical Industry
ACS:	American Cancer Society
ACS:	American Chemical Society
AIOM:	Italian Association for Medical Oncology
AJCC:	American Joint Committee on Cancer
ASCO:	American Society of Clinical Oncology
ASH:	American Society for Hematology
ASTRO:	American Society for Therapeutic Radiology and Oncology
BACR:	British Association for Cancer Research
BASO:	British Association of Surgical Oncologists
BMA:	British Medical Association
BNLI:	British National Lymphoma Investigation
BOA:	British Oncology Association
BODMA:	British Oncology Data Managers Association (UK)
CALGB:	Cancer and Leukemia Group B (USA)
CCG:	Children's Cancer Group (USA)
CCRG:	Children's Cancer Research Group (Oxford, UK)
CCS:	Canadian Cancer Society
COG:	Children's Oncology Group (USA)
COS:	Canadian Oncology Society

CRC:	Cancer Research Campaign (UK)
CSM:	Committee on Safety of Medicines (UK)
EACR:	European Association for Cancer Research
EANO:	European Association for Neuro-Oncology
EBMT:	European Group for Blood and Marrow Transplantation
ECOG:	Eastern Cooperative Group (USA)
EOI:	European Osteosarcoma Intergroup
EORTC:	European Organization for Research and Treatment of Cancer
ESO:	European School of Oncology
ESTRO:	European Society for Therapeutic Radiation and Oncology
FDA:	Food and Drug Administration (USA)
FECS:	Federation of European Cancer Societies
GMC:	General Medical Council (UK)
GPOH:	Gesellschaft für Padiatrische Onkologie und Hamatologie (German Paed. Onc Group)
IACR:	International Association of Cancer Registries
IARC:	International Agency for Research on Cancer
IASLC:	International Association for the Study of Lung Cancer
ICARE:	International Cancer Alliance for Research and Education (ICARE)
ICCCPO:	International Confederation of Childhood Cancer Parent Organizations
ICCG:	International Collaborative Cancer Group
ICCPO:	Icelandic Childhood Cancer Parent Organization
ICH:	International Conference on Harmonization (GCP)
ICRF:	Imperial Cancer Research Fund (UK)
IESS:	Intergroup Ewing's Sarcoma Study (USA)
IMF:	International Myeloma Foundation
INFA:	International Neurofibromatosis Association
IPSO:	International Society of Pediatric Surgical Oncology
ISNCC:	International Society of Nurses in Cancer Care
IWMF:	International Waldenström's Macroglobulinemia Foundation
LREC:	Local Research Ethics Committee (UK)
LRF:	Leukemia Research Fund (UK)
LRFA:	Lymphoma Research Foundation of America
MCA:	Medicines Control Agency (UK)
MRC:	Medical Research Council (UK)
MREC:	Multi-center Research Ethics Committee (UK)
NCCN:	National Comprehensive Cancer Network
NAACCR:	North American Association of Central Cancer Registries
NABCO:	National Alliance of Breast Cancer Organizations
NCCF:	National Childhood Cancer Foundation (USA)
NCI:	National Cancer Institute (USA)
NCIC:	National Cancer Institute of Canada
NCRA:	National Cancer Registrars Association (USA)
NECCR:	North of England Children's Cancer Research Unit

NKCA:	National Kidney Cancer Association (USA)
NNFF:	National Neurofibromatosis Foundation (USA)
NORD:	National Organization for Rare Disorders (USA)
NRCT:	National Registry of Childhood Tumors (UK)
OECI:	Organization of European Cancer Institutes
ONS:	Oncology Nursing Society (USA)
PONF:	Pediatric Oncology Nurses Forum (UK)
SCTN:	Scottish Cancer Therapy Network
SEER:	Surveillance, Epidemiology, and End Results (USA)
SFOP:	French Pediatric Oncology Society
SGDM:	Study Group on Data Management (EORTC)
SGO:	Society of Gynecologic Oncologists
SIOP:	International Society of Paediatric Oncology
SNLG:	Scottish and Newcastle Lymphoma Group
SPOHNC:	Support for People with Oral and Head and Neck Cancer
SWOG:	Southwest Oncology Group (USA)
UKCCCR:	UK Coordinating Committee for Cancer Research
UKCCRG:	UK Children's Cancer Research Group (Oxford)
WHO:	World Health Organization

Common Medical and Prescription Abbreviations (Rx Terms)

Abbreviation	Greek, Latin, or New Latin	Meaning in English
ā	Ante	Before (a with a bar over it)
aa	Ana	of each
AAA		apply to the affected area or abdominal aortic aneurysm
a.c.	ante cibum	before meals
a.c.h.s., ac & hs	ante cibum et hora somni	before meals and at bedtime
a.d.	auris dextra	right ear
ad., add.	adde addatur	Add let there be added, upto
ad.		to; up to
ad lib.	ad libitum	Freely, as much as desired
ad sat.		to saturation
admov.	admove admoveatur	apply [or] add add; let there be added
ad us.	ad usum	according to custom
æq.	æquales	equal
agit.	agita	agitate (stir or shake)
alt. d., alt. dieb.	alternis diebus	every other day; on alternate days

(Continued)

Abbreviation	Greek, Latin, or New Latin	Meaning in English
alt. h., alt. hor.	alternis horis	every other hour; at alternate hours
a.m. (A.M.)	ante meridiem	morning, before noon
amp.	ampulla	ampule
amt		amount
aq.	aqua	water
aq. bull.	aqua bulliens	boiling water
aq. com.	aqua communis	common water
aq. dest.	aqua destillata	distilled water
aq. ferv.	aqua fervens	hot water
a.l., a.s.	auris laeva, auris sinistra	left ear
ALT		alanine aminotransferase
alt.	alternis	alternate
ant.		anterior
ante		before
ap		before dinner
APAP		acetaminophen
aPTT		activated partial thromboplastin
ASA		aspirin
AST		aspartate aminotransferase
ATC		around the clock
a.u. (A.U.)	auris utraque	each ear; both ears
BCP		birth control pills
BDS, b.d.s.	bis die sumendum	twice daily
bib.	bibe	drink
bis	bis	twice
bid, BID, b.d.	bis in die	twice daily
bis ind.	bis indies	twice a day
bis in 7 d.	bis in septem diebus	twice a week
BM		bowel movement
BMI		body mass index
bol		bolus, short-time infusion
BP		blood pressure
BS		blood sugar
BSA		body surface area
BPH		benign prostatic hypertrophy
b.t.		bedtime

(Continued)

Abbreviation	Greek, Latin, or New Latin	Meaning in English
bucc.	bucca	buccal, inside check
cap., caps.	capsula	capsule
cap.	capiat	let the patient take
C.C.		chief complaint
c/o		complaints of
C&S		culture and sensitivity
c.m.	cras mane	tomorrow morning
c.m.s.	cras mane sumendus	to be taken tomorrow morning
Ā, c.	cum	with (usually written with a bar on top of the “c”)
c.c.	cum cibo	with food [or] cubic centimeter
cf.	confer	compare
c.n.	cras nocte	tomorrow night
CABG		coronary artery bypass graft
CAD		coronary artery disease
cochl.	cochleare	spoonful
cochl. ampl.	cochleare amplum	an ample spoonful (a tablespoonful)
cochl. infant.	cochleare infantis	a small spoonful (a teaspoonful)
cochl. mag.	cochleare magnum	a large spoonful (a tablespoonful)
cochl. mod.	cochleare modicum	a modest spoonful (a dessert-spoonful)
cochl. parv.	cochleare parvum	a scant spoonful (a teaspoonful)
colet.	coletur	let it be strained
comp.	compositus	compound
contin.	continuetur	let it be continued
cpt.	capiat	let the patient take
cr., crm		cream
CST		continue same treatment
cuj.	cujus	of which
c.v.	cras vespere	tomorrow evening
cyath.	cyathus	a glassful
cyath. vinos.	cyathus vinosus	a wine-glassful
CBC		complete blood count
CD		controlled delivery
CF		cystic fibrosis
CR		controlled-release

(Continued)

Abbreviation	Greek, Latin, or New Latin	Meaning in English
CV		cardiovascular
CXR		chest X-ray
D, d.	die [or] dosis	days [or] doses
D5LR		dextrose 5% in lactated Ringer's solution (intravenous sugar solution)
D5W, D5W		dextrose 5% in water (intravenous sugar solution)
D5/0.9 NaCl		5% dextrose and normal saline solution (0.9% NaCl)
D5 1/2/NS		5% dextrose and half normal saline solution (0.45% NaCl)
D5NS		dextrose 5% in normal saline (0.9%) (intravenous sugar solution)
D10W, D10W		dextrose 10% in water (intravenous sugar solution)
da	da	give
DAW		dispense as written (i.e. no generic substitution)
D/C, dc, disc.		discontinue or discharge
decoct.	decoctum	decoction
det.	detur	let it be given
dieb. alt.	diebus alternis	every other day; on alternate days
dil.		dilute
dim.	dimidius	one-half
d. in p. æ.	divide in partes æquales	divide into equal parts
div.	divide	divide
d.t.d.	dentur tales doses	give of such doses
dL		deciliter
DS		double strength
DBP		diastolic blood pressure
DKA		diabetic ketoacidosis
DM		diabetes mellitus
DO		Doctor of Osteopathic Medicine
DOB		date of birth
DPT		diphtheria-pertussis-tetanus
DR		delayed-release
DVT		deep vein thrombosis
DTO		deodorized tincture of opium

(Continued)

Abbreviation	Greek, Latin, or New Latin	Meaning in English
DW		distilled water or dextrose in water
elix.	elixir	elixir
e.m.p.	ex modo prescripto	as directed (in the manner prescribed)
emuls.	emulsum	emulsion
et	et	and
EOD		every other day
ex aq.	ex aqua	in water; with water
exhib.	exhibiatur	let it be given
EC		enteric-coated
EENT		eye, ear, nose, and throat
emuls.		emulsion
ER		extended-release
ER		emergency room
f.	fiat	make; let it be made
F		Fahrenheit
f or F		female
f.h.	fiat haustus	make a draught
fl., fld.	fluidus	fluid (liquid)
f.m.	fiat mistura	make a mixture
f. pil.	fiat pilula	make a pill
f.s.a.	fiat secundum artem	make according to art
ft.	fiat	make; let it be made
FBS		fasting blood sugar
Fe		iron
FFP		fresh frozen plasma
ft		foot
g, gm		gram
garg.	gargarisma	gargle
gr.	granum	grain
gtt(s)	gutta(e)	drop(s)
gutt.	gutta(e)	drop(s)
guttat.		drop by drop
GERD		gastroesophageal reflux disease
GI		gastrointestinal
GTT		glucose tolerance test
GU		genitourinary

(Continued)

Abbreviation	Greek, Latin, or New Latin	Meaning in English
H		hypodermic
h, hr, hor.	hora	hour
habet.	habeat	let him have
h/o		history of
hor. alt.	hora alternis	every other hour
hor. decub.	hora decubitus	at bedtime
hor. intermed.	horis intermediis	at intermediate hours
hor. tert.	horis tertiis	every third hour
h.s.	hora somni	at bedtime or half-strength
H&H		hematocrit and hemoglobin
H ₂		histamine 2
HAART		highly active antiretroviral therapy
HCT, or Hct		hematocrit
HCT		hydrocortisone
HCTZ		hydrochlorothiazide
HR		heart rate
HS		half-strength
HTN		hypertension
hx		history
IBW		ideal body weight
ID		intra-dermal
IJ, inj.	injectio	injection
i.m., IM		intramuscular
IN		intranasal
ind.	indies	daily
inf.	infusum	infusion (extraction)/intravenous infusion
i	unus tabuletta	one tablet
ii	duo tabuletta	two tablets
iii	tres tabuletta	three tablets
IO		intraosseous
IP		intra-peritoneal
IR		immediate-release
IT		intra-thecal
IU		international unit
IUD		intrauterine device
i.v., IV		intravenous
i.v.p., IVP		intravenous push

(Continued)

Abbreviation	Greek, Latin, or New Latin	Meaning in English
IVPB		intravenous piggyback
kg		kilogram
L		liter
LA		long-acting
lab		laboratory
lb.	libra	pound
LAS		label as such
lat. dol.	lateri dolenti	to the painful side
l.c.d.	liquor carbonis detergens	coal tar solution
lin	linimentum	liniment
lot.	lotio	lotion
liq.	liquor	liquid (solution)
LMP		last menstrual period
LPN		licensed practical nurse
LR		lactated ringer (solution)
M., m.	misce	mix
mane	mane	in the morning
max.	maximum	maximum
mcg		microgram
MD		medical doctor
mdi		metered-dose inhaler
m.d.u.	more dicto utendus	to be used as directed
mEq		milliequivalent
mEq/L		milliequivalent per liter
mg		milligram
mg/dl		milligrams per deciliter
MgSO ₄		magnesium sulfate
mL		milliliter
mm		millimeter
MM or M		million
mm of Hg		millimeters of mercury
mMol		millimole
MMR		measle-mumps-rubella (vaccine)
mol wt		molecular weight
MR		modified-release
MS		morphine sulfate or magnesium sulfate

(Continued)

Abbreviation	Greek, Latin, or New Latin	Meaning in English
M _{SO} ₄		morphine sulfate
midi		at midday
min.	minimum [or] minim [or] minutum	minimum [or] minim [or] minute
mist.	mistura	mixture
mit., mitt.	mitte	number of tablets provided
mod. præsript.	modo præscripto	in the manner directed
nebul, neb.	nebula	a spray
NMT		not more than
n or noct.	nocte	at night
non rep.	non repetatur	no repeats (no refills)
NPO, n.p.o.	nil per os	nothing by mouth
N/A		not applicable
NAS		intranasal
NDC		National Drug Code
NGT		nasogastric tube
NKA		no known allergies
NKDA		no known drug allergies
noct. maneq.		night and morning
NP		nurse practitioner
NS		normal saline (0.9%)
1/2NS		half-normal saline (0.45%)
NTE		not to exceed
NSAID		nonsteroidal anti-inflammatory drug
o 2, o2		both eyes
O ₂		oxygen
OC		oral contraceptive
o.d.	omni die	every day (once daily)
o.d.	oculus dexter	right eye
OJ		orange juice
o.m.	omni mane	every morning
OM		otitis media
omn. bih	omni bihora	every two hours
omn. hor.	omni hora	every hour
o.n.	omni nocte	every night
OPD		once per day
o.s.	oculus sinister	left eye
o.u.	oculus uterque	both eyes

(Continued)

Abbreviation	Greek, Latin, or New Latin	Meaning in English
OTC		over-the-counter
oz		ounce
p.	perstetur	continue
\bar{p}		after
part. æq.	partes æquales	equal parts
per	per	by or through
p.c.	post cibum	after meals
p.c.h.s., pc & hs	post cibum et hora somni	after meals and at bedtime
Ph.Br., BP	Pharmacopoeia Britannica	British Pharmacopoeia
Ph.Eur.	Pharmacopoeia Europaea	European Pharmacopoeia
Ph.Int.	Pharmacopoeia Internationalis	International Pharmacopoeia
pig./pigm.	pigmentum	paint
p.m.	post meridiem	evening or afternoon
p.o.	per os	by mouth or orally
ppt.	præparata	prepared
p.r., PR	per rectum	rectally
p.r.n., PRN	pro re nata	as needed
pt.	perstetur	continue
pulv.	pulvis	powder
p. v., PV	per vaginam	vaginally
PA		physician assistant
PCA		patient-controlled analgesia
PE		physical exam, pulmonary embolism
per neb		by nebulizer
PFT		pulmonary function tests
PharmD		Doctor of Pharmacy
PMH		past medical history
PT		prothrombin time
PTT		partial thromboplastin time
q	quaque	every, per
q.1 h, q.1 ^o	quaque 1 hora	every one hour
q12h		every 12 hours
q2h		every two hours
q3h		every three hours
q4h		every four hours
q6h		every six hours

(Continued)

Abbreviation	Greek, Latin, or New Latin	Meaning in English
q4PM		at 4 pm (can replace “4” with other numbers)
q.a.d.	quaque alternis die	every other day
q.a.m.	quaque die ante meridiem	every morning (every day before noon)
q.d./q.1.d.	quaque die	every day
q.d.a.m.	quaque die ante meridiem	once daily in the morning
q.d.p.m.	quaque die post meridiem	once daily in the evening
q.d.s.	quater die sumendus	four times a day
q.p.m.	quaque die post meridiem	every evening (every day after noon)
q.h.	quaque hora	every hour
q.h.s.	quaque hora somni	every night at bedtime
q.i.d.	quater in die	four times a day
q.l.	quantum libet	as much as is requisite
q.q.	quaque	each
q.q.h.	quater quaque hora	every four hours
q.s.	quantum sufficiat	a sufficient quantity
q.s.a.d.		add up to
qn		nightly or at bedtime
q.v.	quantum volueris	at will
QWK		every week
qod, QOD, q.o.d.		every other day
RA		rheumatoid arthritis
RDA		recommended daily allowances
rep., rept.	repetatur	repeats
RE		right eye
RN		registered nurse
RL, R/L		Ringer’s lactate
Rx, R _x , RX, R, Rp	recipe	medical prescription or prescription drug
RPh		registered pharmacist
s.	signa	write
̄s	sine	without
s.a.	secundum artem	according to the art (best practice)
SC		subcutaneous
sem.	semen	seed
s.i.d.	semel in die	once a day

(Continued)

Abbreviation	Greek, Latin, or New Latin	Meaning in English
sig.	signa, signetur	write (write on the label)
sing.	singulorum	of each
sig codes		medical or prescription abbreviations
SL, s.l.	sub lingua	sublingually, under the tongue
SOB		shortness of breath
sol.	solutio	solution
s.o.s., si op. sit	si opus sit	if there is a need
s.s., SS	semisse	one-half [or] sliding scale
SSI		sliding scale insulin
SSRI		selective serotonin reuptake inhibitor [or] sliding scale regular insulin
st.	stet	let it stand
stat	statim	immediately
SBP		systolic blood pressure
sum.	sumat [or] sumendum	let him take [or] let it be taken
supf.		superficial
supp.	suppositorium	suppository
susp.	suspensio	suspension
syr.	syrupus	syrup
sp gr		specific gravity
SR		sustained release
STD		sexually transmitted diseases
T		temperature
tab.	Tabella	tablet
tal., t.	talus	such
tbsp.		tablespoon
t.d.s., TDS	ter die sumendum	three times a day
t.i.d., t.d.	ter in die	three times a day
TIA		transient ischemic attack
tid ac		three times a day before meals
TIN, t.i.n.		three times a night
t.i.w.		three times a week
top.		topical
TPN		total parenteral nutrition
tr, tinc., tinct.	tinctura	tincture

(Continued)

Abbreviation	Greek, Latin, or New Latin	Meaning in English
trit.	triturate	grind to a powder
troch.	trochiscus	lozenge
tsp		teaspoon
TO		telephone order
TR		timed-release
TSH		thyroid-stimulating hormone
Tx		treatment
U or u		unit
UA		urinalysis
u.d., ut. dict.		as directed
ung.	unguentum	ointment
USP		United States Pharmacopeia
UTI		urinary tract infection
vag.	vagine	vaginally
vag, p. v.		via the vagina
VLDL		very low-density lipoprotein
vol %		volume percent
vol.		volume
w		with
w/a		while awake
w/f		with food (with meals)
w/o		without
w/v		weight in volume
WBC		white blood cell
WNL		within normal limits
wt.		weight
x		multiplied by
XL		extended-release
YO, y.o.		years old
yr		year
μEq		microequivalent
μg, mcg		microgram
μL		microliter
@		at
>		greater than
<		less than

(Continued)

Abbreviation	Greek, Latin, or New Latin	Meaning in English
lb	libra	pound
ʒ	uncia	ounce
ʒ	drachma	dram (drachm)
℥	scrupulus	scruple
h		hour

The list is for educational purposes only, currently discouraging practices.

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1

An Overview of Cancer

1.1 Introduction

Cancer originates at a cellular level and can occur almost anywhere in the body. Cells are the basic building blocks making up the body, with almost 37 trillion cells in an average human. Normal human cells grow and divide in an orderly process to form new cells as the body requires them. When cells grow old or become damaged, they die, and new cells take their place.

Cancer forms when normal cell processes break down. The safeguards that are characteristic of healthy cells fail, resulting in the cells becoming increasingly abnormal or out of control. Old or damaged cells survive when they should die, and new cells form when they are not required. These extra cells may divide without stopping, forming growths called tumors or cancers. The cancer cells continue to grow and make new cells, resulting in issues in the location where they began (Figure 1.1).

Of the almost 200 different diseases categorized as cancer, most form solid masses of tissue called *tumors*. Blood cancers, such as leukemias, normally do not form solid tumors. However, common to both tumor-forming and non-tumor-forming cancers is uncontrolled, abnormal growth.

Not all tumors are cancers. There are two types of tumors: malignant and benign. Malignant tumors are dangerous, as they can spread into, or invade, nearby tissues. When these tumors grow, a few cancer cells can break away and spread to other parts of the body through the blood or lymphatic system, resulting in the development of new tumors distant from the original tumor.

Benign tumors are not as dangerous. They do not spread into, or invade, nearby tissues or organs. Benign tumors can be large or small. When removed, they usually do not come back, whereas malignant tumors do. Nonetheless, if a benign tumor is located in a sensitive place like the brain, it can still cause some problems.

1.2 Cancer Statistics

Cancer is a major public health problem worldwide and the second leading cause of death after heart disease. Cancer has a huge impact on society in the United

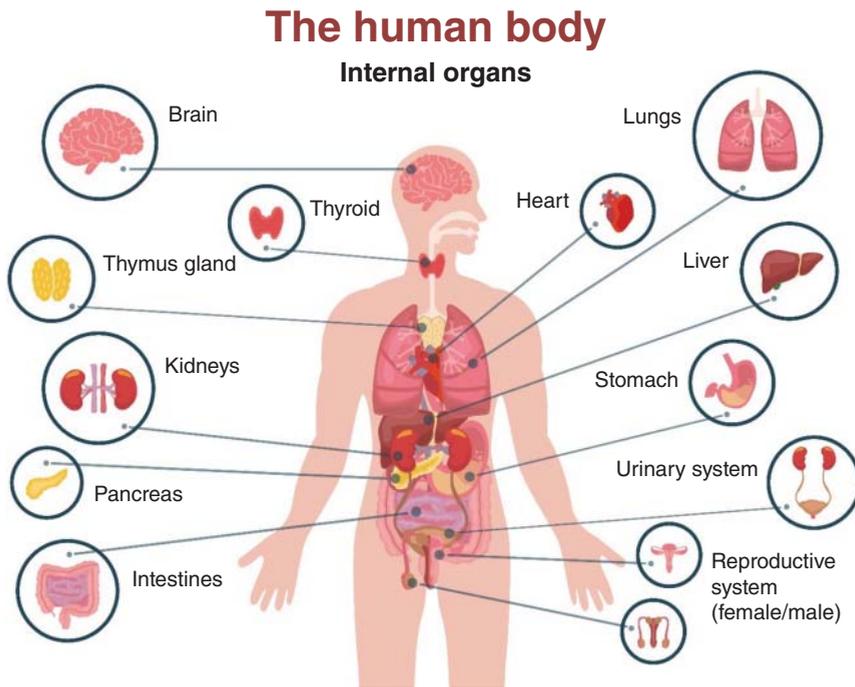


Figure 1.1 The human body contains internal organs and systems, any of which can be the origin of cancer.

States and across the world. Statistical data documents the tremendous numbers of people diagnosed with cancer each year, along with mortality rates. These numbers are further broken down to show the incidence and effects of cancer within various groups defined by age, sex, ethnicity, geographic location, diet, lifestyle, and other factors.

According to the World Health Organization:

- Cancer is the second leading cause of death globally, and is responsible for an estimated 10 million deaths in 2020, and an estimated 19.3 million new cancer cases.
- Globally, about 1 in 6 deaths is due to cancer.
- Approximately, 70% of deaths from cancer occur in low- and middle-income countries.

1.3 Differences Between Normal Cells and Cancer Cells

Cancer cells differ from normal cells (Figure 1.2) in many respects [1–3]:

Appearance: Under a microscope, normal cells and cancer cells look significantly different. Cancer cells often display much more variability in cell size, with some larger than or smaller than normal cells.

Normal cells and cancer cells

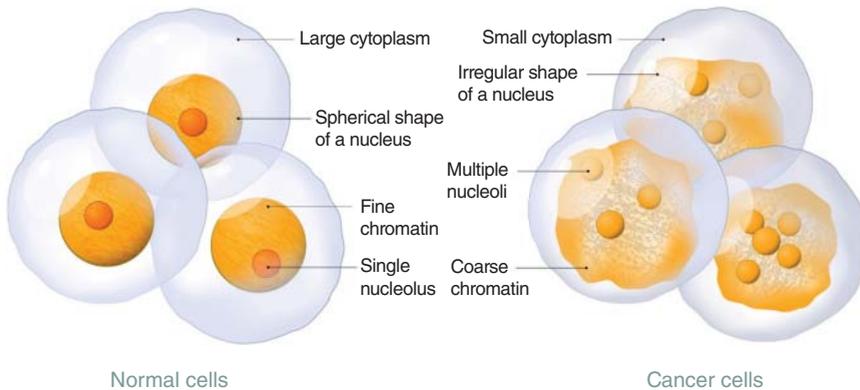


Figure 1.2 Cancer cells are less organized than normal cells and grow in an uncontrolled fashion.

Growth: Normal cells stop reproducing when enough are present. For instance, if cells are required to repair a cut in the skin, new cells are no longer produced when there are enough cells present to fill the gap. Cancer cells, however, do not stop growing and reproducing, and their continuous growth results in the formation of a tumor.

Communication: Cancer cells don't interact with other cells in the same way as normal cells. Normal cells respond to signals sent from other nearby cells to stop growing. Cancer cells do not respond to these signals.

Cell repair and cell death: Regular cells are repaired or die (in a process called *apoptosis*) when they are damaged or get old. Cancer cells either are not repaired or do not undergo apoptosis. The p53 gene regulates cell repair and apoptosis. When this gene is mutated or inactivated, a tumor begins.

Stickiness: Normal cells produce substances that keep them cohesive within a group, as opposed to cancer cells, which do not produce these substances and can therefore spread to other body locations via the bloodstream or lymphatic system.

Ability to metastasize (spread): Normal cells remain in the same area of the body where they serve a particular function, e.g. kidney cells remain in the kidneys. Due to their lack of cohesion, cancer cells are able to move through the bloodstream and lymphatic system to other locations of the body. In these new locations, they have the ability to metastasize, forming tumors distant from the original tumor.

Rate of growth: Normal cells reproduce themselves in a controlled, orderly process, but cease reproducing when enough cells are present. Cancer cells reproduce at abnormal rates, often rapidly and with no stopping mechanism.

Maturation: Normal cells mature with age, whereas cancer cells remain immature and continue to reproduce unchecked before they are fully mature.

Evade the immune system: The human body's immune system is a network of organs, tissues, and specialized cells that keeps the body protected from infections and other harmful conditions. When normal cells become damaged, the immune system identifies and removes them. Cancer cells are able to evade removal by the immune system, resulting in the formation of tumors.

Energy source: In the presence of oxygen, normal cells produce most of their energy supply. Cancer cells have changed, however, and are able to produce energy without oxygen. This capacity to generate energy for growth and survival without oxygen (a condition found inside a tumor) enables cancer cells to thrive where normal cells die.

1.4 Types of Cancer

There are more than 200 types of cancer, with researchers classifying them based on the location of origin [4]. Four major types of cancer are:

1.4.1 Carcinomas

This is the most common type of cancer. A carcinoma starts in the skin or in the tissue that covers the surface of internal organs and glands. Carcinomas normally form solid tumors. Examples include prostate cancer, breast cancer, lung cancer, and colorectal cancer.

1.4.2 Sarcomas

A sarcoma occurs in the tissues that support and connect the body, including fat, muscles, nerves, tendons, joints, blood vessels, lymph vessels, cartilage, or bone.

1.4.3 Leukemias

Leukemia is blood cancer that occurs when healthy blood cells change and develop uncontrollably. The four main types of leukemia include acute lymphocytic leukemia, chronic lymphocytic leukemia, acute myeloid leukemia, and chronic myeloid leukemia.

1.4.4 Lymphomas

Lymphomas start in the lymphatic system. The lymphatic system is a network of vessels and glands that protects the human body from infection. There are two main kinds of lymphomas: Hodgkin lymphoma and non-Hodgkin lymphoma.

1.5 The Role of Genes and Chromosomes

In the nucleus of each cell, there are the thread-like structures that package deoxyribonucleic acid (DNA) called **chromosomes**. Chromosomes are found in all living cells and consist of a single molecule of DNA bound to various proteins (Figure 1.3). They carry the **genes**, which are the basic units determining inherited traits. Genes control cell function, particularly how cells grow and divide, and when they need to stop this growth [5–14].

In the human body, there are 46 chromosomes, arranged in 2 sets of 23. We inherit one set from our mother and one from our father. Chromosomes contain all the information for the physical characteristics that make up an individual. One chromosome in each set determines whether a person is female or male. The other 22 chromosome pairs decide other physical characteristics in the human body. These chromosome pairs are also called autosomes.

Genes regulate protein production. Each protein functions on its own and also carries messages for the cell. Each gene follows specific instructions, encoded in their genetic material, for producing proteins; each protein performs specific functions for the cell (Figure 1.4).

Cancers start when one or more genes mutate. Mutations, however, are a normal occurrence. Their results may be beneficial, harmful, or neutral, depending on the location within the gene where the change has taken place. Most of the time the body corrects the mutations and nothing unusual happens.

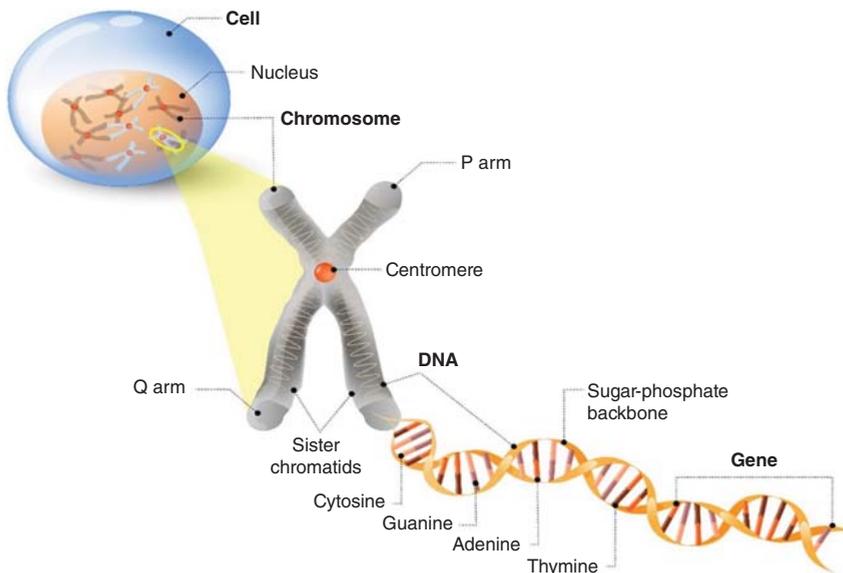


Figure 1.3 Cell structure showing DNA in the nucleus. The DNA molecule is a double helix. A gene is a length of DNA that codes for the manufacture of a specific protein.

Transcription and translation

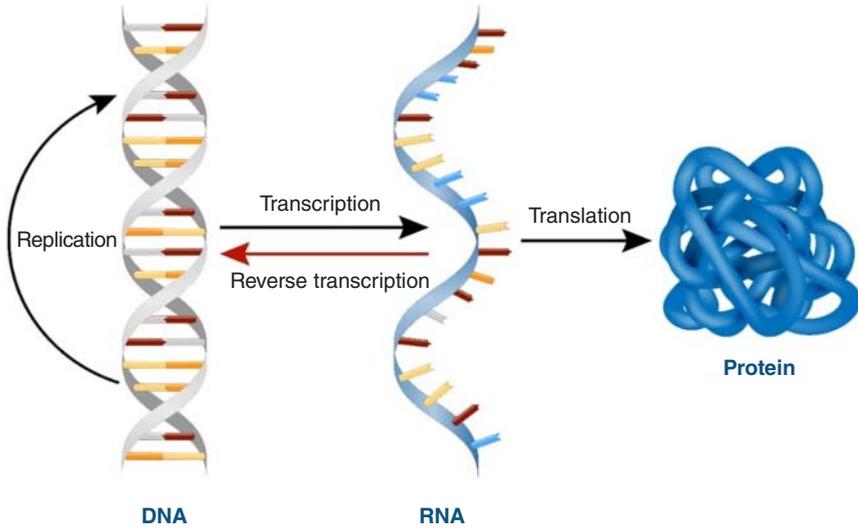


Figure 1.4 Information from DNA is used to make proteins from genes.

A single mutation will generally not produce cancer. Typically, cancer develops from multiple mutations over a lifetime, which is why cancer occurs more frequently in older people. Mutations have had more opportunities to occur the longer a person lives. Mutation of genetic material changes the instructions for protein formation, resulting in the production of an abnormal protein or sometimes prevention of a certain protein being formed. An abnormal protein cannot carry out its specific function correctly, possibly leading to uncontrolled cell multiplication and the start of cancer (Figure 1.5).

Process of cancer cell development

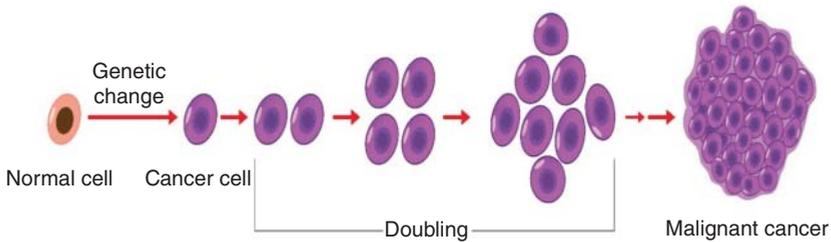


Figure 1.5 Cancer cells start as normal cells, which acquire mutations over time that change them to cancer cells.

1.6 Genetic Mutations

There are two basic types of genetic mutations:

1.6.1 Acquired Mutations

Mutations of this type are the most common cause of cancer, and when this occurs, it is called *sporadic cancer*. These mutations, initially affecting only a few cells in the body, damage the genes in these cells. Since these mutations are acquired, they do not pass from parents to children. Major factors contributing to acquired mutations include:

- Tobacco
- Ultraviolet (UV) radiation
- Viruses
- Age

1.6.2 Germline Mutations

Not as common as acquired mutations, germline mutations take place in reproductive cells, such as those in a female's egg or a male's sperm. Offspring resulting from the union of reproductive cells with germline mutation receive that mutation, which is copied into every cell in the body as it develops. Since these mutations are in the reproductive cells, they are carried from generation to generation and are known as **inherited cancers**. Germline cancers comprise between 5 and 20% of all cancers.

Germline cancers should not be confused, however, with **germ cell tumors**, which start in the cells that give rise to sperm or eggs. These tumors can develop almost anywhere in the body, and they can be either benign or malignant.

1.7 Genes Connected to Cancer

Certain types of genes have been linked to the development of cancer in the human body. Scientists categorize these genes in broad groups:

1.7.1 Tumor Suppressor Genes

The genes have the protective feature of controlling cell growth by:

- Monitoring new cell divisions
- Correcting DNA sequences that have mutated
- Controlling cell death (apoptosis)

Examples include *TP53* (tumor protein 53 or cellular tumor antigen p53, or referred to as *p53*), *PTEN*, *RBI*, and *APC*. When tumor suppressor genes mutate, cell growth is unchecked and may result in tumor formation.

In the case of germline mutations, if certain tumor suppressor genes – namely *BRCA1* or *BRCA2* – mutate, there is a higher chance of developing hereditary breast

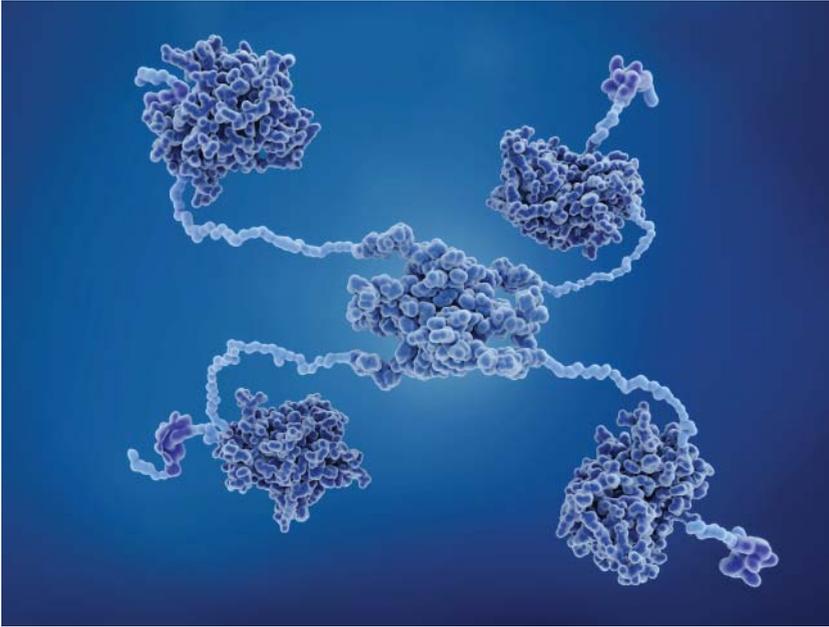


Figure 1.6 Structure of p53 tumor suppressor protein. p53 prevents cancer formation and acts as a guardian of the genome. Mutations in the *p53 gene* contribute to about half of the cases of human cancer. Source: Juan Gärtner/Adobe Stock.

or ovarian cancer for women, and prostate cancer for men. These specific mutations also have been linked to an increased risk of pancreatic cancer and melanoma.

More than half of diagnosed cancers are caused by mutations that damage or disable gene *p53* (Figure 1.6). This is a common acquired mutation. Much more rarely, germline *p53* mutations occur with subsequent greater risk for many types of cancer in family members.

1.7.2 Oncogenes

These genes change healthy cells into cancerous ones with acquired mutations. Examples of common oncogenes include *HER2* (human epidermal growth factor receptor 2) and genes in the *RAS family*. *HER2* is a specialized protein found in certain cancerous cells, including those in the breast and ovaries, where it oversees the growth and spreading of the disease. Another family of genes, referred to as *RAS*, manufactures proteins that interfere with cell communication pathways, as well as cells' growth and death.

1.7.3 DNA Repair Genes

These genes take care of mistakes that occur during the process of DNA replication. Usually, these are tumor suppressor genes. If an error occurs in a DNA repair gene itself, however, its important correction function ceases, and errors in DNA copies

can be mutations that might lead to cancer. Mutations in tumor suppressor genes (including *BRCA1*, *BRCA2*, and *p53*, which are all DNA repair genes) or oncogenes create the greatest likelihood of cancer occurring. *Lynch syndrome* is one of many genetic conditions originating from hereditary DNA repair gene mutations. Mutations of DNA repair genes can also be acquired.

Scientists know a lot about how cancer genes work. Many cancers, however, are not linked to one specific gene, but more likely result from multiple gene mutations. In addition, some studies suggest that genes interact with their environment, further complicating the current understanding of the role genes play in cancer. Each person's cancer has a unique combination of genetic changes, and as cancer develops, additional mutations occur. Even within same cancer, different cells may have different genetic alterations.

Given the earlier complexity, scientists continue to study how genetic changes affect cancer development. This information has led to improvements in cancer treatment, including early detection, risk reduction, the use of targeted therapy, and survival. Further research will provide additional understanding and a better overall outlook on the effects of this disease.

1.8 Tumors and Metastasis

As mentioned earlier, cancer starts when gene mutations interfere with the normal, orderly process of cell division. Cells begin to grow uncontrollably without stopping, sometimes forming a mass of tissue called a tumor. Tumors can be cancerous or benign. As previously mentioned, a cancerous tumor is malignant, meaning it can grow large and extend to other locations of the body. A benign tumor can become larger over a period of time, but will not spread to other parts of the body.

Metastasis is the medical term for cancer that appears in a different organ than where it originated from. When this occurs, scientists say the cancer has metastasized. Other terms referring to metastasis are metastatic cancer and stage 4 cancer. Some types of cancer do not form a tumor, including leukemias, most types of lymphoma, and myeloma.

One of the first places cancer often metastasizes to is the nearest lymph node(s). A *lymph node* is a tiny, bean-shaped organ that functions in the human body's defense against infection. Lymph nodes are located in clusters in different parts of the body, such as the neck, groin area, and under the arms. Due to lymph nodes being part of a system, which circulates about the entire body, called the *lymphatic system*, cancer cells that reach the lymph nodes can be further transported to other body areas.

Metastases to the bones, brain, liver, lymph nodes, and lungs are very common. Some cancers tend to spread to certain parts of the body. For example, unresolved breast cancer spreads to the bones, liver, lungs, chest wall, and brain, whereas lung cancer tends to extend to the brain, bones, liver, and adrenal glands. Prostate cancer mainly spreads to the bones. Colon and rectal cancers have the greatest chance of spreading to the liver and lungs.

1.9 Hereditary Cancer Risk

In 5–10% of cancers, the major factor are gene mutations, which have been inherited and predispose an individual to developing the disease. Individuals with these inherited genetic mutations, or hereditary cancer syndrome, are at a significantly greater risk of developing associated cancer. The following conditions suggest a possible increased risk:

- **Family history of cancer:** Having three or more relatives on the same side of the family with the same or related forms of cancer.
- **Cancer at an early age:** Having two or more relatives diagnosed with cancer at an early age. This factor may differ depending on the type of cancer.
- **Multiple cancers:** Having two or more types of cancer occurring in the same relative.

The possibility of heredity cancer is one reason why health screening questionnaires contain questions about cancer (and other illnesses) affecting extended family members.

Genetic Testing. If a person meets any of the criteria indicating they may have a heightened risk for developing cancer, an option they might wish to consider is genetic testing. Choosing to undergo genetic testing is a personal decision made for various reasons, but best made in collaboration with others, including other family members, one's physician, and a genetic counselor.

Currently, consideration of genetic testing is recommended in the following cases:

- A personal or family history suggests a genetic cause of cancer.
- A test will yield clear results regarding changes in a specific gene or genes.
- The results will help with the diagnosis or management of a condition. This might guide someone at higher risk to counteract it with such steps as surgery, medication, frequent screening, or lifestyle changes.

Genetic counselors are very instrumental both in deciding whether or not to undergo genetic testing, as well as conferring with about the test findings. The counselor can explain the pros and cons of genetic testing, help people cope with the process of completing the testing, and give advice regarding ways to lower cancer risk in the future.

1.10 Cancer Screening and Diagnosis

Screening tests to aid physicians in the detection and diagnosis of cancer fall into one of four general types. Doctors conduct a physical examination to check for signs of any health abnormalities or indicators of disease, such as external lumps or localized pain. A thorough physical exam includes a review of the patient's family history of the disease, health history, and lifestyle factors, all of which may contribute to the development of cancer [15–36].

Laboratory tests, both routine and specialized, consist of an analysis of samples of tissue, blood, urine, or other bodily substances, to check for the presence

of certain chemicals, abnormal cells, etc. A variety of **imaging procedures** are also available to give physicians a look at organs, bones, and other internal body structures. As mentioned earlier, **genetic testing** can provide information about specific gene mutations (changes) associated with certain types of cancer.

Before undergoing any screening tests, it is important to know the risks involved with the tests themselves, as some cancer screening tests pose more risk than the potential benefit. It should be ascertained whether the screening has actually been proven to reduce the chance of dying from cancer. Bleeding or other problems can result from certain types of screening procedures. For example, screening for colon cancer with sigmoidoscopy or colonoscopy can cause tears in the lining of the colon, leading to internal bleeding.

In addition, cancer screening test results may be abnormal even though there is no cancer present, which is called a **false-positive test result**. A false-positive result causes patient anxiety and usually follow-up with more tests and procedures, which may have additional risks. On the other hand, test results sometimes indicate no cancer even though the disease is present. A person who receives a **false-negative test result** may delay seeking medical care even if there are other abnormal symptoms.

Many screening tests have been shown to detect cancer at an early, more treatable stage and thereby reduce the risk of dying from this disease. The following is a list of a few types of cancer frequently encountered in modern societies, along with tests used to screen for them:

1.10.1 Colon Cancer

Colonoscopy, *sigmoidoscopy*, and *high-sensitivity fecal occult blood tests* (FOBTs) have all been proven to decrease deaths from colorectal cancer. Colonoscopy and sigmoidoscopy also help prevent colorectal cancer because they detect abnormal colonic growths (polyps), which can be removed at that time before they develop into cancer. In addition, there are screenings for colon cancer in low-risk patients using a stool sample, offering an alternative to the risks associated with, and the preparation for, a colonoscopy.

Virtual colonoscopy, also called *CT colonography* or *computed tomography*, is an imaging procedure in which a radiologist uses X-rays and a computer to create images of the rectum and colon from outside the body. Ulcers, polyps, and cancer can be detected using this test.

1.10.2 Lung Cancer

Low-dose *helical computed tomography* has been shown to decrease lung cancer deaths among heavy smokers aged 55–74 years.

1.10.3 Breast/Cervical/Ovarian/Endometrial Cancers

Mammography screening produces an X-ray image of breast tissue and has been shown to significantly reduce mortality from breast cancer among women aged 40–74, especially those aged 50 or older.

In addition to mammography, physicians recommend all adult women obtain regular *clinical breast examinations* and perform *breast self-examinations* at home, checking for unusual lumps or thicknesses in the breast tissue, or any other unusual breast symptoms. These physical exams have also been proven to reduce breast cancer mortality rates.

Regarding the possible presence of cervical cancer, Pap tests (or Pap smears) and human papillomavirus (HPV) testing decrease the risk of cancer by identifying and treating abnormalities in cells before they become cancerous. Overall, these tests have resulted in decreased deaths from cervical cancer. Testing is generally recommended starting at the age of 21 and continued at regular intervals until a female reaches 65 years, at which time they can be curtailed if recent results have been normal.

For females who have been identified as carrying a harmful mutation in the *BRCA1* or *BRCA2* gene, indicating an increased risk for breast and other types of cancer, physicians may recommend magnetic resonance imaging (MRI) of their breasts.

Mutations in *BRCA1* or *BRCA2* genes also predispose females to ovarian or endometrial cancer, and in cases where these mutations are evidenced, a *transvaginal ultrasound* is utilized to obtain an image of females' ovaries and/or uterus. The *CA-125 blood test* is sometimes used alongside a transvaginal ultrasound for early detection of ovarian cancer, particularly in those having an increased risk of developing this disease. CA-125 is a cancer antigen, which can be elevated in the presence of ovarian cancer. Furthermore, evidence of someone having an inherited cancer syndrome called *Lynch syndrome* makes them predisposed to endometrial cancer in particular, along with several other specific cancers.

1.10.4 Prostate Cancer

For early detection of prostate cancer, physicians perform a *digital rectal exam* and a blood test called a *prostate-specific antigen (PSA) test*. PSA is a chemical produced by the prostate gland, and elevated levels of it in the blood may indicate the presence of prostate cancer, although not definitely.

1.10.5 Liver Cancer

In people with increased risk for liver disease, doctors may suggest an ultrasound of the liver and possibly an *alpha-fetoprotein (AFP) blood test*. AFP is a protein produced by the liver, and an elevated level of it in the blood can indicate the presence of liver cancer.

1.10.6 Skin Cancer

People who are at risk for skin cancer, and those who live in climates with sunshine much of the year, are advised to examine their skin regularly or have this done by a health care provider. Prompt reporting of skin changes, such as a new mole

or change in the appearance of a preexisting mole, can lead to early detection of skin cancer.

1.11 Cancer Treatment Options

Currently, there are many kinds of cancer treatments available, depending on the type of cancer and how advanced it is. Some cancer patients only require one type of treatment, whereas others may need more than one – including surgery, chemotherapy, medication, or radiation therapy – provided in a variety of specific combinations and timings [37–82].

1.11.1 Surgery

It is the physical removal of cancer from the body. In some cases, this may be a simple outpatient procedure, requiring an hour or two in a specialist’s office. In other cases, it may involve a major operation with a few nights in the hospital and intense therapy treatments afterward.

“Clear margins” is a term well known for its association with cancer surgery. When the cancerous tissue is taken out, it is ideal to have a “clear margin” (clear of cancerous matter) surrounding the affected area targeted during the surgery. Depending on the location of the cancer, specific measurements are used to define “clear” in this regard. Basically, since cancer cells may have been in contact with tissues around them, surgeons take a section of healthy tissue around the cancerous parts in order to be certain all of the cancer has been removed.

Preparation for cancer surgery varies depending on the procedure. The surgeon’s office contacts patients well in advance to go over special instructions, not only for what to do beforehand, but also for what to expect on the day of surgery and during recovery afterward. Many large hospitals even provide cancer patients access to local networks offering counseling, housing, and other services for patients and their relatives during treatments.

1.11.2 Radiation Therapy

It is another modality of cancer treatment during which high-intensity radiation is used to kill cancer cells and shrink tumors [48, 49]. Depending on several factors, such as the location of cancer, and the age and health of the patient, radiation can be an effective therapy. It is often used in conjunction with other treatment methods, e.g. reducing the size of a tumor prior to surgery or irradiating diseased bone marrow before a transplant.

Radiation treatments take place in special facilities, with the number and length of each dose taking place in accordance with each individual’s treatment plan. Specialists monitor patients’ response to treatment and often adjust the plan to best meet an individual’s needs.

Side effects of treatment also vary according to the individual, with hair loss, fatigue, nausea, and vomiting being among the most common. Some patients don't experience any of these, have different side effects, or even have none at all.

1.11.3 Chemotherapy

It uses drugs to kill cancer cells. The chemicals used are cytotoxic, i.e. capable of halting the replication or growth of cancer cells, resulting in cell death [47, 53, 56]. Depending on the type of cancer and how the chemotherapy is combined with other treatments, it can come in many forms – pills, liquids, or injectables administered at home or under supervision in a facility. The specific cancer-killing agent used, and the number and length of treatments, varies according to the type of cancer and the special circumstances of each patient, including their response to the therapy. Although chemotherapy drugs are designed to kill cancer cells, which reproduce more rapidly than normal cells, healthy tissues can also, unfortunately, be affected. This gives rise to certain side effects, which also vary by individual. The most common are hair loss, fatigue, nausea, and vomiting. Again, though, not all patients experience these particular effects, and may encounter different ones entirely or even none at all.

1.11.4 Targeted Therapy

It is similar to chemotherapy in that it utilizes drugs to attack and kill cancer cells; however, targeted therapy is designed to work specifically on mutated proteins found only in the cancer cells, thereby reducing the potential damage to other healthy tissues. Targeted therapy is often used in combination with other treatment modalities [53–55, 57, 60, 67]. Although a seemingly ideal method to eliminate cancer, it still requires exposure to powerful chemicals, which can result in side effects such as hair and skin problems and high blood pressure.

1.11.5 Immunotherapy

It is a relatively new treatment option compared to surgery, radiation, and chemotherapy. Over the past few decades, scientists have discovered new ways to boost the human body's immune response to cancer. Currently, immunotherapy consists of either stimulating the immune system to more effectively overcome cancer or supplementing the immune system with special synthetic proteins or other tools that work against cancer cells [47, 52, 53, 62, 63]. An example of immunotherapy is the development of the HPV vaccine, which is now recommended by the US Centers for Disease Control and Prevention (CDC).

1.11.6 Hormone Therapy

It is a consideration for some cancers, such as breast or prostate cancer, that are sensitive to hormones. Drugs are available, which block the body's normal signals to

produce certain hormones, preventing hormone-dependent cancers from continued growth. Although this sounds simple, any drugs that change the natural processes of the body include risk of side effects. Hormone therapy is frequently used with other treatments, and specialists work with each patient to determine when and how to administer it, the amount and duration of doses, and to gauge individual responses to treatment [65, 66].

1.11.7 Stem Cell Transplant

It is a method used to restore the body's ability to produce new blood cells after a patient has undergone other forms of aggressive cancer treatment [5]. For certain types of cancer, very high doses of chemotherapy or radiation are required to destroy the cancer cells, but cells that produce blood are also destroyed in the process. In this case, stem cells are administered along with a blood transfusion. Stem cells are collected either from the patient before cancer treatment or from a donor. After stem cell treatment, it takes two to four weeks for an individual's body to recover and begin producing blood cells again. As with other treatments, there are risks involved, including the possibility that the stem cells will not settle in the bone marrow and begin producing blood cells as intended. When that occurs, it is deemed a failed treatment, and the process may be repeated.

1.11.8 Precision Medicine

It differs from other forms of cancer treatment in that it is focused on genetic changes particular to each individual's cancer to determine the most effective treatment options for countering it. Although precision medicine may involve various forms of traditional cancer treatment, it considers the genetic particularities of each individual's cancer to offer a more specialized treatment plan [68–74].

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2

Cancer Risk Factors and Prevention

2.1 Introduction

Nearly one-third of all cancer deaths are related to: (i) individuals having a high body mass index (BMI), which is a measure of body fat based on height and weight of males and females; (ii) eating a diet low in fruits and vegetables; (iii) use of tobacco and alcohol; and (iv) lack of physical activity.

Cancer prevention therefore includes adopting behaviors and habits that reduce the risk of developing cancer, such as maintaining a healthy lifestyle, avoiding exposure to known cancer-causing substances, getting recommended cancer screenings, and taking medicines or vaccines that can prevent many types of cancer from developing [1–136].

2.2 Hormones

Estrogens are a group of hormones that function in human sexual and reproductive development, mostly in women. Although these hormones have essential physiological roles in both sexes, they have also been linked with an increased risk of many cancers. For example, undertaking combined menopausal hormone therapy, consisting of estrogen plus progestin (a synthetic version of the female hormone progesterone), can increase the risk of breast cancer in women. Menopausal hormone therapy using estrogen alone may increase the risk of endometrial cancer, and it is used only in women who have had a hysterectomy. Women considering menopausal hormone therapy should discuss possible risks and benefits with a medical specialist.

Researchers have discovered that a woman's risk of breast cancer is related to the estrogen and progesterone produced by her ovaries, which are known as endogenous estrogen and progesterone [1–12]. Exposure to a high level of these hormones, or over a lengthy period of time, has been associated with an increased risk of developing breast cancer. High levels of exposure can be caused by starting menstruation early, going through menopause late, having a first pregnancy late in life, or never giving birth. Conversely, however, giving birth is also a protective factor with regard to developing breast cancer.

Regarding cervical cancer, it has been demonstrated that using birth control pills may increase a woman’s risk of developing this type of cancer. However, there is also evidence linking birth control pills with lower frequency of other types of cancer, such as endometrial (uterus), colorectal, and ovarian.

2.3 Immunosuppression and Infectious Agents

Infection by certain environmental pathogens can significantly weaken the body’s immune system, rendering it less able to detect and destroy cancer cells or to fight off infections that are linked to cancer. Human immunodeficiency virus (HIV) is one such pathogen, and people with this condition are at risk of developing several cancers. Those with HIV/AIDS have an increased risk of cancers that are caused by infectious agents, including Epstein–Barr virus (EBV), hepatitis B (HBV) and hepatitis C (HCV) viruses, infections that can cause liver cancer, human herpesvirus 8 (also known as Kaposi sarcoma-associated virus), and human papillomavirus (HPV) (Figure 2.1), which has been associated with cervical, anal, oropharyngeal, and other cancers [14–16].

Most of the viruses associated with the possible start of cancer can be spread from one person to another through blood and/or other body fluids. By avoiding “risky behaviors,” people can lower their chance of infection. One important preventative measure is getting immunized. The HBV vaccine is recommended for certain high-risk adults, including adults who are sexually active but not in a mutually

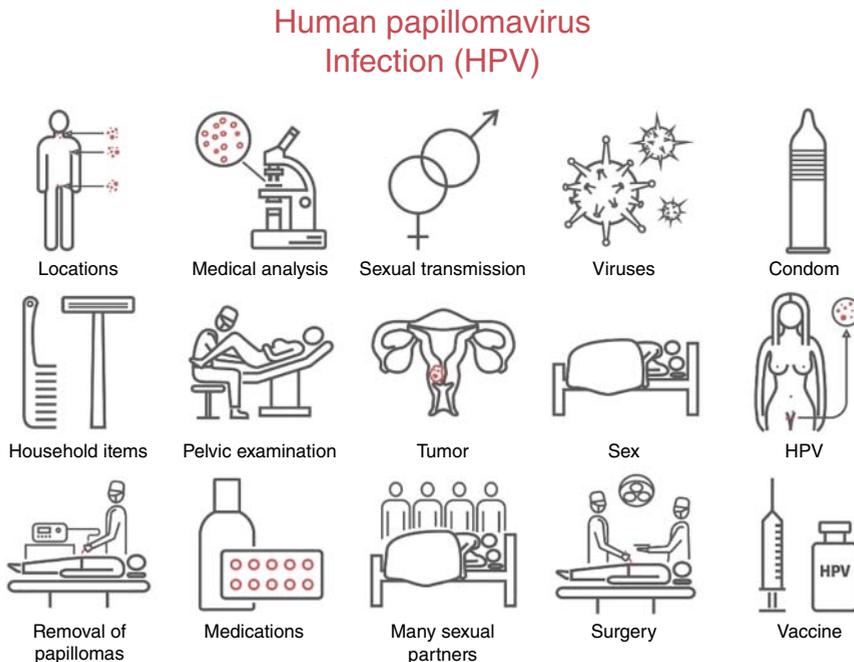


Figure 2.1 HPV infection causes several types of cancers.

monogamous relationship, people with sexually transmitted infections, intravenous drug users, men who have sex with other males, and health care or public safety workers who might be exposed to infected blood or body fluids. There is also an HPV vaccine, which is recommended for all girls and boys aged 11 and 12, and available to anyone aged 26 or younger who did not avail themselves of the vaccine as adolescents.

Other practical ways to reduce exposure to pathogens linked to cancer development are having safe sex, and in the case of drug users, not sharing hypodermic needles. The more sexual partners an individual has during his or her lifetime, the greater are the chances of contracting sexually transmitted infections like HIV or HPV. Safe sex consists of limiting the number of sexual partners and using a condom. For intravenous drug users, sharing needles with an infected person poses the risk of contracting HIV or infection with hepatitis B or C.

People who receive organ transplants sometimes take medications to suppress the immune system so that the body will not reject the organ. These drugs are immunosuppressive, and like environmental pathogens, weaken the body's immune system so they cannot adequately destroy cancer cells or resist infections associated with cancer.

Transplant recipients have a higher risk of developing several different types of cancers, some of which are directly linked to infectious agents, and others not. The four most common cancers among transplant recipients, which develop more frequently in these individuals than in the general population, include non-Hodgkin lymphoma (NHL), lung, kidney, and liver cancers. NHL has been shown to be associated with EBV infection.

In addition to certain viruses, infections by some bacteria and parasites can cause cancer or increase its likelihood (Figure 2.2). Viruses can disrupt the cell signaling network that normally controls cell growth and proliferation. Several of these infectious agents can also cause chronic inflammation that may lead to the development of certain types of cancers.

2.4 Chronic, Long-term, DNA-damaging Inflammation

Inflammation is part of the body's response to injury or infection, a way of protecting damaged tissue so that healing can ensue. Signs of inflammation vary depending on where they occur. Inflammation can be acute (diminish relatively quickly) or chronic. Long-term or chronic inflammation can result from certain conditions, including rheumatoid arthritis, asthma, periodontitis, active hepatitis, ulcerative colitis, or even obesity. Unfortunately, chronic inflammation can damage DNA and thus lead to a higher risk of cancer.

2.5 Being Overweight/Obese

People who have excess fat on their body may have an increased risk of many types of cancer (Figure 2.3), including cancers of the breast (in postmenopausal women),



Figure 2.2 Cancer-causing pathogens: *Helicobacter pylori*, hepatitis B virus (HBV), hepatitis C virus (HCV), and human papillomavirus (HPV).

colon, rectum, endometrium (lining of the uterus), esophagus, kidney, pancreas, and gallbladder [16–18].

Reducing the risk of these types of cancers involves eating a healthy diet, being physically active, and maintaining a healthy weight (BMI). Practicing these beneficial habits also lowers the risk of other diseases like heart disease, type 2 diabetes, and high blood pressure. Another positive effect is the reduction of depression that comes about with responsible self-care.

2.6 Eating to Win

Lowering cancer risk through healthy eating is a form of prevention not only of cancer but also of many serious physical and mental issues. In modern societies, it is entirely possible to adjust one's diet to include many more vegetables, fruits, whole grains, and other fiber-rich foods (Figure 2.4). Protein sources can be found in fish and certain vegetables, and these are preferable over animal sources.

Healthy, cancer-fighting choices include the following:

Health risks of obese people

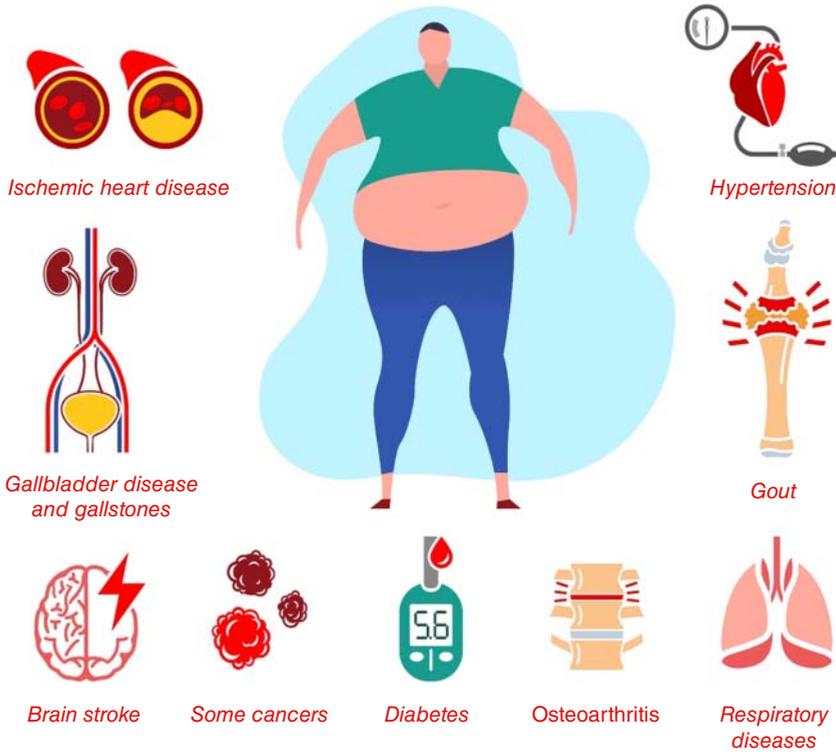


Figure 2.3 Cancers and other diseases related to being overweight.

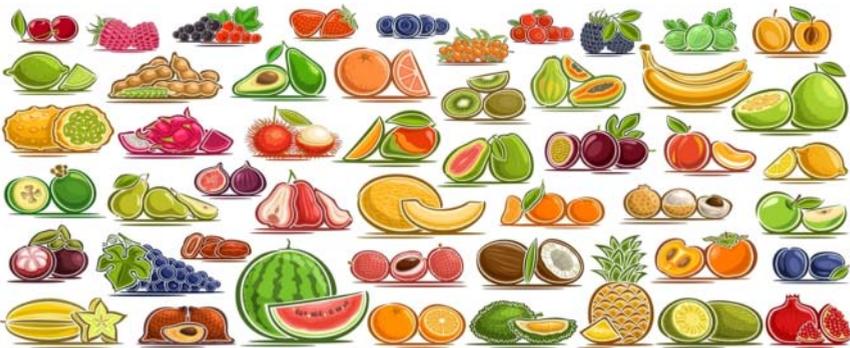


Figure 2.4 Healthy foods.

2.6.1 Vegetables

Broccoli, cauliflower, fresh peas, spinach, brussels sprouts, lettuce, tomato (fresh, no salt added), garlic, ginger, edamame, bok choy, onion, kale, cabbage, green beans, asparagus, radish, leek, beet, avocado, cucumber, bell pepper, eggplant, okra, zucchini, cilantro, lime, lemon, carrot, squash, sweet potato (limit amount), moringa leaf, and bitter melon.

2.6.2 Fruits

Orange, grapefruit (basically, all citrus fruits), grapes, all kinds of berries (strawberry, blueberry, acai berry, cranberry), apricot, pear, apple, plum, kiwi, cherry, papaya, mango, pomegranate, banana, guava, watermelon, cantaloupe, honeydew, peach, coconut, pineapple (no sugar added), jackfruit, lychee, cherimoya, starfruit, persimmon, and longan.

2.6.3 Grains

Rice (white and brown), whole grain, and lentil.

2.6.4 Proteins

Lean chicken or turkey (small quantities and not every day), lean fish, eggs (limit quantity, not every day), tofu, bean (garbanzo bean, kidney bean, soybean, black bean, pinto bean, and navy bean with no added salt), chickpea, lentil.

2.6.5 Bread

Whole grain bread.

2.6.6 Cereal

Oatmeal, bran flakes, rice, wheat, and corn (maize).

2.6.7 Dairy

Low-fat milk, yogurt, and low-fat cheese.

2.6.8 Snacks

Popcorn, hummus, whole grain chips, unsalted nuts such as peanuts, almonds, cashews, walnuts, and pistachios.

2.6.9 Beverages

Water (minimum eight cups daily), juices (100% is best, minimize added sugar), green/black/white tea, and coffee.

2.6.10 Spices

Olive oil, canola oil, turmeric powder, cumin, coriander, black pepper, green chilli, cinnamon, curry leaf, fennel seed, green cardamom, mint, basil, saffron, sesame seed, and parsley.

2.7 Role of Sugar and Artificial Sweeteners on Cancer

Although there is no scientific evidence that eating sugar is a direct cause of cancer, the overconsumption of sweets often results in consuming an excess number of calories, leading to overweight and obesity. Having too much body fat is associated with many forms of cancer, as discussed previously. Doctors recommend eating nutritious and filling foods, including whole grains, vegetables, fruits, and beans, and replacing sugary beverages with low- or no-calorie drinks. It is also helpful to drink lots of water to help flush any toxic chemicals from the body.

As a side note, for people who already have cancer, there is no confirming evidence that eating sugar will make their cancer worse, or that if they stop eating sugar, their cancer will shrink or disappear. However, the same precaution involving the contribution of sugar to excess body fat applies.

Regarding artificial sweeteners, researchers have done numerous studies of sugar substitutes such as saccharin (Sweet'N Low®, Sugar Twin®, and Necta Sweet®), cyclamate, aspartame (Equal®, NutraSweet®), acesulfame potassium (Sunett® and Sweet One®), sucralose (Splenda®), and neotame, and found no evidence that they cause cancer in humans. With the exception of cyclamate, all of these artificial sweeteners have been approved by the Food and Drug Administration for sale in the United States.

2.8 Role of Certain Foods and Drinks on Cancer

If possible, the intake of these types of foods should be minimal.

2.8.1 Processed Meat and Fish

According to the World Health Organization (WHO), processed meats like hot dog, ham, bacon, sausage, and some deli meats can cause cancer (Figure 2.5). Their carcinogenic effect is related to these foods being treated in some way to preserve or flavor them, such as by salting, curing, fermenting, or smoking.

Salt-cured fish, popular in China, is high in nitrates and nitrites, which have been shown to be carcinogens in animal testing and may cause cancer in humans. These chemical compounds can damage DNA, leading to cancers of the head and neck.

Furthermore, the WHO has reported that any kind of red meat may be linked to an increased risk of colorectal cancer. There are studies suggesting red meat contributes to pancreatic and prostate cancers, although the evidence is not as conclusive.



Figure 2.5 Processed foods cause cancer. Source: Pixel-Shot/Adobe Stock.

2.8.2 Alcohol

According to the American Institute for Cancer Research, there is now strong evidence that drinking alcohol increases the risk of developing several forms of cancer, including those of the mouth, pharynx, larynx, esophagus, liver, breast, stomach, and colorectum [19–35]. Drinking even small amounts regularly was shown to increase the risk of specific cancers, such as breast (Figure 2.6).

For cancer prevention, it is suggested that alcohol consumption be eliminated. However, since alcohol has also been shown to have certain health benefits, including reducing heart disease and type 2 diabetes, guidelines have been modified to drinking two alcoholic beverages per day for men, and one per day for women.

Once in the body, ethanol is easily oxidized to acetaldehyde. DNA bases such as purine and pyrimidine are nucleophiles and react with acetaldehyde resulting



Figure 2.6 Drinking alcohol causes cancer. Source: LIGHTFIELD STUDIOS/Adobe Stock.

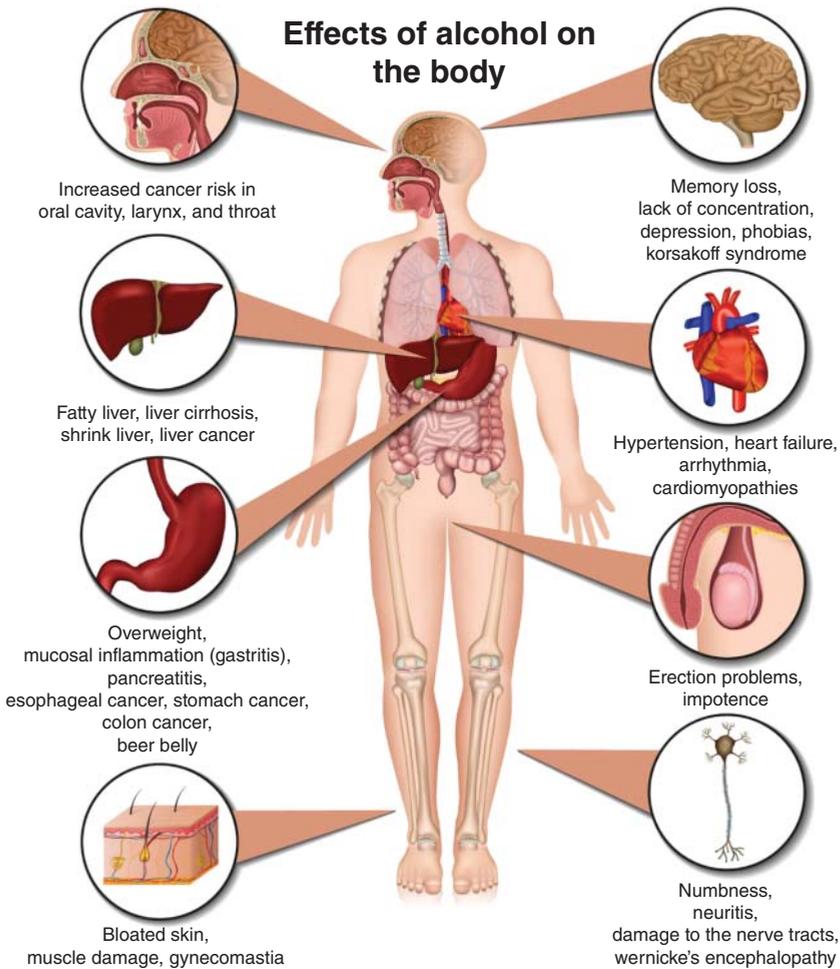


Figure 2.7 Bodily long-term effects of alcohol consumption.

in DNA damage inside cells. Alcohol and its byproducts damage the liver leading to inflammation and scarring (cirrhosis). Though liver cells try to repair the damage, yet they can end up with mistakes in their DNA, which can lead to cancer (Figure 2.7).

2.9 Role of Smoking or Tobacco Use on Cancer

Tobacco use is one of the leading causes of cancer and cancer mortality. People who smoke or use tobacco products, or who are regularly around environmental tobacco smoke known as “secondhand smoke,” have a proven, increased risk of developing cancer. Tobacco products contain more than 70 chemicals that damage DNA [36–72]. According to the Centers for Disease Control and Prevention (CDC),

Negative effects of cigarette smoking

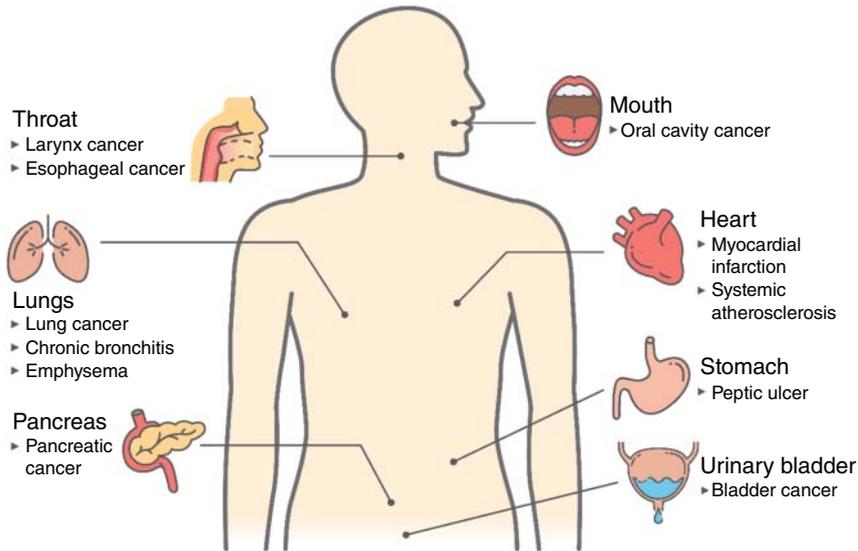


Figure 2.8 Negative bodily effects of smoking.

nonsmokers exposed to secondhand smoke at home or at work increase their risk of developing lung cancer by 20–30%.

Tobacco use has been linked to several types of cancer, including that of the lungs, larynx (voice box), mouth, esophagus, throat, bladder, kidney, liver, stomach, pancreas, colon and rectum, and cervix, as well as acute myeloid leukemia (Figure 2.8). Even people who use smokeless tobacco (snuff or chewing tobacco) are more susceptible than nontobacco users to cancers of the mouth, esophagus, and pancreas.

There is no safe level of tobacco use, and it is recommended that anyone using any kind of tobacco product stop immediately. The tobacco industry has been known to minimize the risk, but obviously, an individual consumer's health is not their priority. Fortunately, those who quit smoking, regardless of their age and gender, increase their life expectancy substantially over people who continue to smoke. Furthermore, quitting smoking at the time of a cancer diagnosis significantly reduces an individual's risk of dying.

2.10 Role of Radiation on Cancer

Radiation of certain wavelengths, called ionizing radiation, has enough energy to damage cellular DNA and thereby cause cancer. Examples of ionizing radiation are radon, X-rays, gamma rays, alpha particles, beta particles, and solar ultraviolet (UV) rays (discussed next). Although X-rays are frequently used for diagnostic purposes in



Figure 2.9 Role of radiation on cancer. Source: Image Supply Co/Adobe Stock.

humans, the amount of exposure from them is not considered enough of the cancer risk to justify avoiding routine X-ray screenings for potentially more life-threatening conditions (Figure 2.9). The studies demonstrating the association between radiation and cancer tend to involve extremely high exposure levels, like those in a nuclear disaster, or the intense radiation sometimes needed to treat people who already have cancer. Nevertheless, the American Cancer Society cautions that “there is no threshold below which this kind of radiation is thought to be totally safe.”

Visible light and the energy from cell phones and electromagnetic fields are lower-energy, nonionizing forms of radiation. They do not affect DNA and have not been linked to developing cancer.

2.11 Role of Sunlight and UV Radiation on Cancer

The sun, sunlamps, and tanning booths all produce UV radiation. Too much exposure to UV radiation damages the skin, resulting in early signs of aging and an increased risk of skin cancer (Figure 2.10). Although these effects are more common among people with light skin tone, individuals with any color skin can develop skin cancer [77, 78].

People of all ages and skin tones are recommended to limit the amount of time they spend in the sun, especially between 10:00 am and 4:00 pm, when the sun’s rays are the most intense. Keep in mind that UV radiation is reflected by sand, water, snow, and ice, and it can penetrate windshield and window glass. For anyone planning to be outside for over 15 minutes, it is advisable to apply sunscreen generously and repeatedly, stay in the shade as much as possible, and wear protective clothing. Tightly woven, loose-fitting clothes that cover most areas of exposed skin work



Figure 2.10 Role of sunlight on cancer. Source: muhor/Adobe Stock.

best. Choose bright or dark colors as these reflect more UV radiation than pastels or bleached fabrics.

Other sources of UV radiation, such as tanning beds, should also be avoided (Figure 2.11). According to the Skin Cancer Foundation, people who use a tanning bed before age 35 increase their chance of developing melanoma (skin cancer) by 75%.



Figure 2.11 Role of tanning beds on cancer. Source: gstockstudio/Adobe Stock.

2.12 Role of Radon on Cancer

Radon (Rn) is a radioactive, colorless, odorless, tasteless noble gas, given off by rocks and soil as the radioactive element radium (Ra) breaks down. Radium, which is formed when the radioactive elements uranium (U) and thorium (Th) break down, was discovered by Marie and Pierre Curie in 1898. People who are exposed to high levels of radon may have an increased risk of lung cancer [80, 81].

Some parts of the United States have higher levels of radon in their rocks and soil, and for this reason, affordable radon test kits have been developed to assess the amount of this gas in individual homes. The test kits are available at most hardware stores. There are several ways to reduce home radon to a safe level.

2.13 Known Human Carcinogens

2.13.1 Arsenic, Coal Tar, Coal-tar Pitch, Diesel, Asbestos, Formaldehyde, and Air Pollutants

Arsenic is a widely distributed, natural element found in the Earth's crust. In its inorganic form, it is toxic to the human body and a known carcinogen [82]. It reaches people through contaminated drinking water in less-developed countries such as Bangladesh, and it can find its way into food produced from crops irrigated with arsenic-contaminated water (Figure 2.12).

The WHO estimates that at least 140 million people in 50 countries drink water containing high levels of arsenic. In addition, arsenic is one of the cancer-causing agents in tobacco.

Coal tar and coal-tar pitch are coal derivatives widely used for various commercial and industrial purposes. Research findings suggest that miners who are



Figure 2.12 Arsenic causes cancer. Source: darkoudovicic/Adobe Stock.



Figure 2.13 Coal exposure can cause cancer. Source: Anzelm/Adobe Stock.

exposed to the process of coal gasification and other occupational workers involved (Figure 2.13) with coal tar or coal-tar pitch suffer significantly higher rates of skin cancer and cancers of the lungs, bladder, kidney, and digestive tract [83, 84].

Diesel exhaust from the burning of diesel oil has over 30 components (Figure 2.14) that can cause various types of cancer, according to the International Agency for Research on Cancer [85–95].

Fracking is the process of drilling down into the lower layers of the earth and injecting liquid at high pressure, in order to force open existing fissures and extract oil or gas (Figure 2.15). During this technique, however, cancer-causing compounds including benzene and formaldehyde may be released into the air and groundwater [96].

Asbestos is a naturally occurring mineral substance that has a fibrous structure. For this reason, it can be pulled into a fluffy consistency. Asbestos was used as an insulation material (Figure 2.16) for years before the dust was linked to lung cancer [98]. It is also linked to mesothelioma, another serious and potentially fatal disease (see later chapter on Mesothelioma).

Products that contain asbestos are not completely banned in the United States, though the Environmental Protection Agency (EPA) regulates their use.

Formaldehyde is a chemical compound used as a constituent of certain building materials and some types of glue, as well as a preserving agent and disinfectant (Figure 2.17). Scientists have known for years that formaldehyde can cause nasal cancer in rats, and the International Agency for Research on Cancer reports that it is a carcinogen for humans also [99–104].

Air pollution is defined as the presence of poisonous chemicals or compounds (organic or inorganic) in the air we breathe, at levels that pose a health risk.



Figure 2.14 Exposure of diesel exhaust can cause cancer. Source: Alexandr Mitic/Adobe Stock.



Figure 2.15 Exposure to fracking can cause cancer.



Figure 2.16 Exposure to asbestos causes lung cancer. Source: Profotokris/Adobe Stock.



Figure 2.17 Formaldehyde can cause cancer. Source: betka82/Adobe Stock.

Air contaminated with pollution, which can exist as particulates, biological molecules, or gases, can lead to various types of cancer [105, 106]. One example is soot, which is contaminated carbon particles resulting from incomplete burning of organic material. Even as long ago as the 1770s, chimney sweeps in London were developing scrotal cancer at higher rates than in the general population. Inhalation of soot has also been linked to lung, esophageal, and bladder cancers.

2.13.2 Certain Types of Plastic

These can be dangerous in terms of exposing humans to carcinogenic substances, especially when plastic containers become scratched or cracked, allowing chemicals to be leached out. One example is *bisphenol A* (BPA), a synthetic estrogen that has been used in many plastics and resins since the 1960s. BPA resins can be used inside products like metal food cans as sealants, while polycarbonate BPA plastics can include water bottles and food storage containers. BPA can even be found in thermal paper receipts, where it is used to stabilize the ink.

The safety of BPA has been controversial, as studies have found it is linked to obesity, diabetes, problems with fertility and reproductive organs, susceptibility to various cancers, and cognitive/behavioral deficits like attention deficit hyperactivity disorder (ADHD).

While many plastic manufacturers have started labeling their products “BPA-free,” the compound is still very commonly used in a broad array of consumer products.

2.13.3 Acrylamide

It is a chemical mainly used to make substances called polyacrylamide and acrylamide copolymers, which are used in several types of industrial processes, including the production of paper, dyes, and plastic. They are also found in some consumer items like caulking and food packaging.

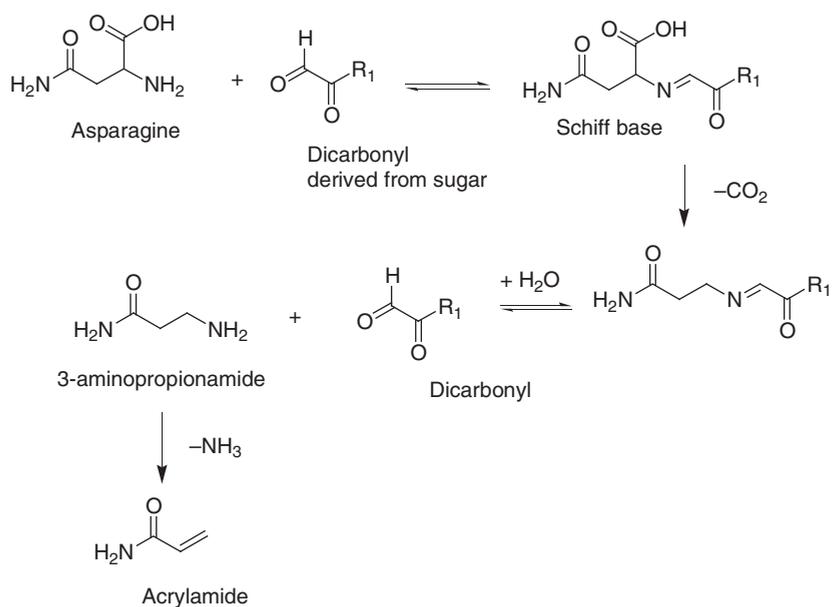
In addition, acrylamide is found in some foods. The main foods containing acrylamide are French fries and potato chips, crackers, bread, cookies, breakfast cereals, canned black olives, prune juice, and coffee. It can be created when vegetables that contain the amino acid asparagine are heated to high temperatures in the presence of certain sugars. The browning of meat generates acrylamide as a byproduct of the chemical reaction called the **Maillard reaction**, which occurs during the browning process (Figure 2.18) between asparagine and reducing sugar [123–126]. The carbonyl group of the sugar reacts with the amino group of the amino acid to form an *N*-substituted glycosylamine, which undergoes Amadori rearrangement to produce a ketosamine. The open-chain ketosamine further undergoes dehydration and deamination steps to give a reactive dicarbonyl compound. This dicarbonyl reacts with an asparagine to produce a Schiff base, which further degrades through Maillard reaction to produce toxic acrylamide (Scheme 2.1). Acrylamide can react with cysteine or lysine and damage normal DNA.

Tobacco smoke from cigarettes, however, is a much more significant source of exposure to acrylamide than food.

In studies using rodent models, acrylamide exposure was linked to an increased risk of developing several types of cancer [107–117]. According to the National Toxicology Program’s Report on Carcinogens, acrylamide is likely carcinogenic based on its effect in laboratory animals given drinking water contaminated with this compound. More studies, however, need to be done to find out the levels and length of exposure required to affect humans.



Figure 2.18 Browning of meat produces acrylamide and it can cause cancer.



Scheme 2.1 Formation of acrylamide, a byproduct of Maillard reaction between reducing sugars and amino acids.

Certain occupations involve more employee contact with cancer-causing substances. Some workers are exposed daily. A few occupations at higher risk include aluminum workers, painters, tar pavers (who are exposed to carcinogenic benzene), rubber and plastic manufacturers, hairdressers, and manicurists in nail salons.

2.14 Possible Human Carcinogens

A carcinogen is any substance that promotes carcinogenesis, the formation of cancer. An English physician John Hill first observed in 1761 that certain chemical exposures have been linked to the development of cancer [118]. He noted that the snuff users developed nasal cancer more frequently than the general population. Over 100 000 chemicals are used, and about 1000 new chemicals are listed each year, but not all chemicals are carcinogens. These chemicals are found in everyday items, including as foods, personal products, packaging, prescription drugs, and household and lawn care products [119–122]. While some chemicals may be harmful, not all contact with chemicals is dangerous to your health. Examples of known human carcinogens are asbestos, arsenic, benzene, beryllium, cadmium, nickel, vinyl halides, and others. Examples of possible human carcinogens are chloroform, DDT, polycyclic aromatic hydrocarbons, aromatic amines, azo dyes, nitrosamines and nitrosamides, hydrazo and azoxy compounds, carbamates, halogenated compounds, natural products, and others. DNA bases such as purine and pyrimidine are nucleophiles and react with any electrophiles resulting in DNA damage. Some reactive chemicals such as alkylating agents (alkyl halides), aldehydes, and others directly make a covalent bond with nucleophilic sites in the purine and pyrimidine rings of nucleic acids. Some chemicals react with DNA after being metabolized by the liver cytochrome P450 enzymes. For example, some alkenes and polycyclic aromatic hydrocarbons are metabolized by human liver enzymes to produce an electrophilic epoxide. DNA attacks the epoxide and is bound permanently to it and damages normal cells.

An estimation of some factors contributing to cancer development and their relative significance is shown in (Figure 2.19).

2.15 Guidelines for Early Detection of Cancer

The following are the current American Cancer Society guidelines for early detection of cancer in most men and women:

Women aged 20–29:	Breast exam and Pap test (for cervical cancer) every 1–3 yr.
Women aged 30–39:	Mammograms (X-rays of the breast) every 1–3 yr, Pap test and HVP test every 5 yr.
Women aged 40–49:	Breast test every year, Pap and HPV test every 5 yr.
Women aged 50–75:	Mammograms every year, Pap and HPV test every 5 yr, colonoscopy every 10 yr, colon CT scan every 5 yr. ^{a)}

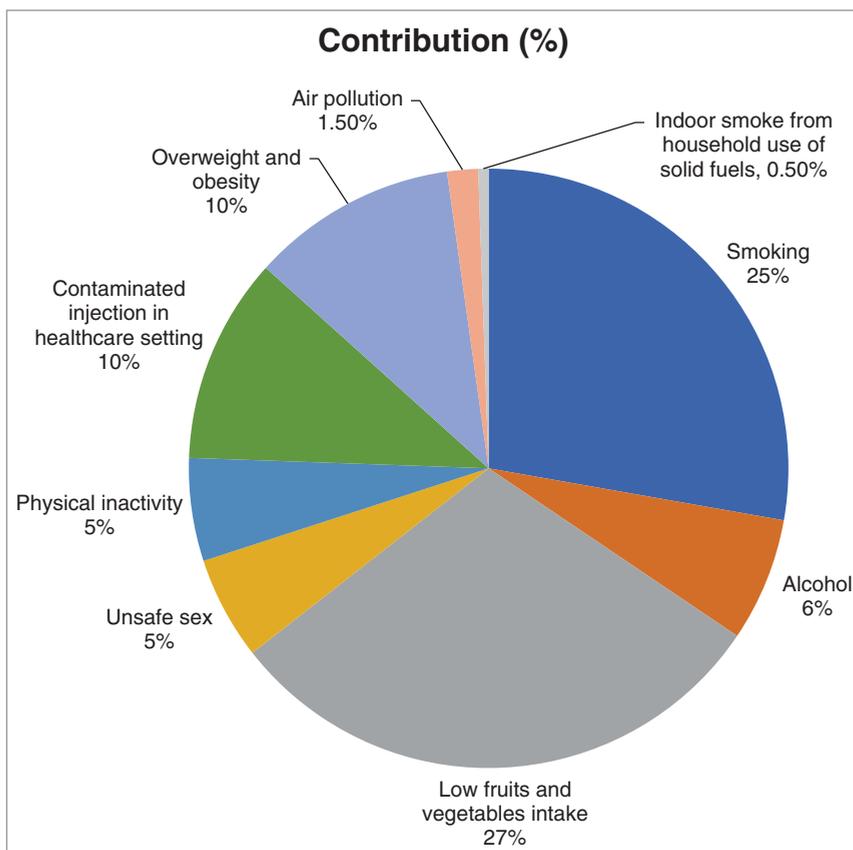


Figure 2.19 Factors contributing to cancer development and their relative significance.

Women aged 76+:	Your doctor will decide.
Men aged above 50:	Prostate cancer test and colonoscopy every 10 yr.
All adults aged 50–75:	If smoking, testing for lung cancer every year; if not smoking and in good health, testing for lung cancer every 10 yr.

- a) Women at the time of menopause should consider testing for endometrial cancer. Any unexpected vaginal bleeding or spotting should be reported to a physician immediately.

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3

Bladder Cancer

3.1 Introduction

The bladder is a hollow, flexible, pouch-like organ located in the pelvis. The bladder's main function is to store urine, which is made in the kidneys before it is excreted from the body. The tubes that carry urine from the kidneys to the bladder are the ureters, and when urine is excreted, the muscles in the bladder propel it out through another tube called the urethra.

Cells inside the bladder can mutate and grow out of control, and a tumor can form over time [1–57]. Untreated, cancer in the bladder (Figure 3.1) can spread to distant parts of the body like the lymph nodes, bones, lungs, and liver. According to the National Cancer Institute, bladder cancer is the sixth most common cancer in the United States, with an estimated 81 190 new cases diagnosed in 2018, resulting in 17 240 deaths.

3.2 Genes Associated with Bladder Cancer

Currently, tobacco smoking is the main known contributing factor in the development of urinary bladder cancer [9, 10, 39], with some cases appearing to involve mutations in the genes *HRAS*, *KRAS2*, *RB1*, *FGFR3*, *PIK3CA*, *KDM6A*, and *TP53*. These genes contribute critical roles in regulating gene activity and cell growth, ensuring cells do not grow and divide too rapidly or uncontrollably. Possibly the mutations in these genes break normal gene regulation, contributing to the uncontrolled cell growth resulting in tumor formation in the bladder.

3.3 Types of Bladder Cancer

- (i) **Urothelial carcinoma**, also called transitional cell carcinoma, occurs inside the bladder, developing in the cells that line the urinary tract. It is by far the most common type of bladder cancer.

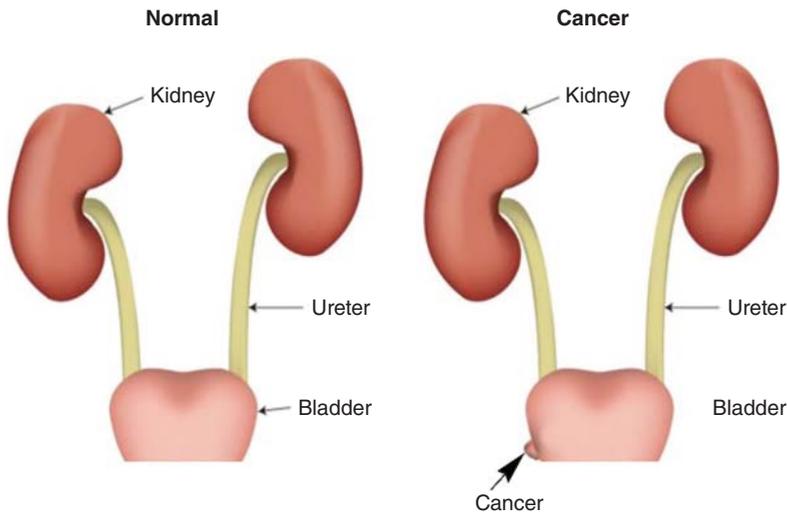


Figure 3.1 Bladder cancer.

- (ii) **Squamous cell carcinoma** occurs when ongoing irritation results in squamous cells forming in the bladder lining, which can then become cancerous.
- (iii) **Adenocarcinoma** is very rare and develops from glandular cells.

3.4 Symptoms of Bladder Cancer

- Blood in the urine
- Pain or burning sensation during urination
- Low back pain
- Frequent urination
- Color variation in urine
- Painful urination
- Urge to urinate, even when the bladder is not full
- Weak or very low-volume urine flow
- Polyuria (producing an abnormally high volume of dilute urine)
- Family history

3.5 Diagnosis

The following current diagnoses are available (Based on [15–19, 23, 26, 35]):

- **Urinalysis** is performed to detect blood or any other substances indicative of abnormality.
- **Urine cytology** is the procedure whereby urine is checked for the presence of cancer cells.
- **Urine culture** is completed in a laboratory and checks for possible viral or bacterial species in the urine.

- **Urine tumor marker tests** are designed to detect substances released by bladder cancer cells.
- **Biopsy**
- **Imaging tests**

3.6 Methods of Treatment

There are several treatment options available [3, 5, 7, 20, 24, 30, 31, 34, 38, 39, 41–112].

3.6.1 Surgical Transurethral Resection of Bladder Tumor (TURBT)

It is the most common surgery for early-stage bladder cancer. During this operation, a bladder tumor is removed by way of the urethra.

3.6.2 Radiation Therapy

Targeted radiation is used to kill cancer cells.

3.6.3 Photodynamic Therapy

In this relatively new treatment for early bladder cancer, particular types of drugs are administered, which make cancer cells more sensitive to light. This is followed by light therapy to destroy tumor cells.

3.6.4 Chemotherapy

Specialized drugs are used before or after surgery to kill the cancer cells. Common chemotherapy agents used are cisplatin, carboplatin, doxorubicin, fluorouracil, gemcitabine, methotrexate, mitomycin, paclitaxel, thiotepa, valrubicin, and vinblastine. Chemotherapy drugs are used alone or in combination. It depends on what they are being used for, a person's overall health, and other factors.

3.6.5 Targeted Therapy

Erdafitinib, fibroblast growth factor receptor (FGFR) inhibitor is used to treat locally advanced or metastatic bladder cancer that has certain mutations (changes) in the *FGFR2* or *FGFR3* gene.

3.6.6 Immunotherapy

It is also known as biologic therapy; this treatment involves stimulating the body's own immune system to attack cancer cells. Examples include atezolizumab (Tecentriq), avelumab (Bavencio), nivolumab (Opdivo), pembrolizumab (Keytruda), enfortumab vedotin (Padcev), and sacituzumab govitecan (Trodelvy).

3.7 Treatment Regimens

Single-agent Regimens

Atezolizumab

1200 mg IV on day 1

Repeat cycle every 21 days [68–71].

Avelumab

10 mg/kg IV over 60 minutes' infusion on day 1

Repeat cycle every 14 days and continue until disease progression or unacceptable toxicity [72–74].

Docetaxel (adjuvant therapy)

75 mg/m² IV on days 1, 8, 15, 22, 29, and 36

Repeat cycle every six weeks [75–77].

Docetaxel (advanced stage)

100 mg/m² IV on day 1

Repeat cycle every 21 days [75–77].

Durvalumab

10 mg/kg IV on day 1

Repeat cycle every 14 days [78–80].

Enfortumab vedotin-ejfv

1.25 mg/kg (up to a maximum of 125 mg for patients \geq 100 kg) IV infusion over 30 minutes on days 1, 8, and 15 of a 28-day cycle

Continue until disease progression or unacceptable toxicity [81].

Epirubicin

50 mg/m² IV once on days 1, 8, 15, 22, 29, and 36

Repeat cycle every six weeks [82, 83].

Erdafitinib

8 mg orally once daily, with a dose increase to 9 mg once daily based on serum phosphate levels and tolerability at 14–21 days [84, 85].

Gemcitabine

1200 mg/m² IV infusion over 30 minutes on days 1, 8, and 15

Repeat cycle every 28 days [62, 86, 87].

Mitomycin-C

4 mg/ml (up to 15 ml, 60 mg) via ureteral catheter once weekly for six weeks [88]

Nivolumab

240 mg IV over 30 minutes' infusion every two weeks or 480 mg every four weeks

Continue until disease recurrence or unacceptable toxicity for up to one year [89–91].

Paclitaxel

250 mg/m² IV infusion over 24 hours on day 1
Repeat cycle every 21 days.

or

80 mg/m² IV infusion over three hours on days 1, 8, 15, and 22
Repeat cycle every 28 days [65, 92, 93].

Pembrolizumab

200 mg IV every three weeks or 400 mg every six weeks
Continue until disease progression or unacceptable toxicity or up to 24 months [61, 94–97].

Pemetrexed

500 mg/m² IV on day 1
Repeat cycle every 21 days. Initiate folic acid 400–1000 µg orally once daily, starting seven days before the first dose of pemetrexed. Administer vitamin B12, 1 mg intramuscularly, one week prior to the first dose of pemetrexed, and every three cycles thereafter [98].

Do not substitute oral vitamin B12 for intramuscular vitamin B12.

Thiotepa

60 mg in 30–60 ml of sodium chloride injection into the bladder by catheter, once a week for four weeks. The course may be repeated if necessary. It is used for the treatment of superficial papillary carcinoma of the urinary bladder [99].

Valrubicin

800 mg administered intravesical once a week for six weeks. For intravesical use only. Do *not* administer by intravenous or intramuscular routes [100].

Combination Regimens**5-Fluorouracil + Mitomycin C + Radiation Therapy**

5-Fluorouracil: 500 mg/m² IV continuous infusion on days 1–5
Mitomycin-C: 12 mg/m² IV on day 1
Radiation therapy: 275 cGy/day, five days per week
Chemotherapy is given at the same time with radiation therapy [58].

Docetaxel + Cisplatin

Docetaxel: 75 mg/m² IV on day 1
Cisplatin: 75 mg/m² IV on day 1
Repeat cycle every 21 days for six cycles [101].

Gemcitabine + Cisplatin

Gemcitabine: 1000 mg/m² IV over 30 minutes on days 1, 8, and 15
Cisplatin: 75 mg/m² IV over 60 minutes on day 1
Repeat cycle every 28 days [60, 102].

Gemcitabine + Carboplatin

Gemcitabine: 1000 mg/m² IV over 30 minutes on days 1 and 8

Carboplatin: AUC of 4–6, IV over 30 minutes on day 1

Repeat cycle every 21 days for 4–6 cycles [103–105].

Gemcitabine + Docetaxel

Gemcitabine: 800 mg/m² IV over 30 minutes on days 1, 8, and 15

Docetaxel: 60 mg/m² IV on day 1

Repeat cycle every 28 days [106].

Gemcitabine + Paclitaxel

Gemcitabine: 1000 mg/m² IV over 30 minutes on days 1, 8, and 15

Paclitaxel: 200 mg/m² IV over three hours on day 1

Repeat cycle every 21 days [107, 108].

Dose-Dense Gemcitabine + Cisplatin

Gemcitabine: 2500 mg/m² IV on days 1 and 8

Cisplatin: 35 mg/m² IV on days 1 and 2

Repeat cycle every two weeks for six cycles [109].

CMV

Cisplatin: 100 mg/m² IV over 60 minutes on day 2, given second

Methotrexate: 30 mg/m² IV on days 1 and 8, given first

Vinblastine: 4 mg/m² IV over 10 minutes on days 1 and 8

Repeat cycle every 21 days [3].

ITP

Ifosfamide: 1500 mg/m² IV over three hours on days 1–3 with mesna

Paclitaxel (Taxol): 200 mg/m² IV infusion over three hours on day 1

Cisplatin (Platinol): 70 mg/m² over two hours on day 1

Repeat cycle every 3–4 weeks for a maximum of six cycles [111]. Granulocyte colony-stimulating factor was administered with each cycle.

MCV

Methotrexate: 30 mg/m² IV on days 1, 15, and 22

Carboplatin: AUC of 4.5, IV over 60 minutes on day 1

Vinblastine: 3 mg/m² IV over 10 minutes on days 1, 15, and 22

Repeat cycle every 28 days [103].

Dose-Dense MVAC (DD-MVAC)

Methotrexate: 30 mg/m² IV on days 1, 15, and 22

Vinblastine: 3 mg/m² IV over 10 minutes on days 2, 15, and 22

Doxorubicin (Adriamycin): 30 mg/m² IV on day 2

Cisplatin: 70 mg/m² IV over 60 minutes on day 2

Repeat cycle every 28 days [59, 112].

3.8 Risk Factors/Possible Prevention

- (i) If you smoke, stop. Scientists believe tobacco products cause about half of all bladder cancer cases [10, 11, 40].
- (ii) Drink plenty of fluids, especially water. During urination, the body sheds harmful chemicals that build up in our bladder.
- (iii) Eat more fruits and vegetables. Studies show that eating lots of fruits and green leafy vegetables, particularly those containing selenium like carrots, asparagus, and raw broccoli, reduce the risk for many types of cancer, including bladder cancer.
- (iv) Avoid overconsumption of fatty foods.
- (v) Be aware of family history.
- (vi) Avoid occupational exposure to certain chemicals, including benzidine and 2-naphthylamine, which are also found in cigarette smoke.
- (vii) Avoid drinking water that contains arsenic. Even at very low levels, drinking a lot of water with this contaminant can lead to cancer.

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4

Cancers of the Blood

4.1 Introduction

Blood is a specialized bodily fluid consisting of four major components: plasma, red blood cells, white blood cells, and platelets. Blood has several roles in the human body, but its three main functions are transport, protection, and regulation.

Transport. Blood functions in the transport of the following:

- Oxygen (O₂) and carbon dioxide (CO₂) between the lungs and the rest of the body.
- Nutrients from the digestive tract and storage sites to the rest of the body.
- Waste products to be detoxified and/or removed by the liver and kidneys.
- Hormones from the glands in which they are produced to their target cells.

Protection. Blood supports the immune system, playing important roles in inflammation, the body's response to injury or infection:

- Leukocytes, or white blood cells, kill invading microorganisms and cancer cells.
- Antibodies and other proteins destroy pathogenic substances.
- Platelet factors initiate blood clotting to prevent excess blood loss.

Regulation. Blood regulates:

- pH by interacting with acids and bases. Blood itself has a slightly basic pH of 7.35–7.45.
- Water balance, by transporting water to and from body tissues.
- Body temperature. Blood functions in maintaining the body's average temperature of 98.6 °F.

4.2 Genes Associated with Blood Cancer

Cancers of the blood, also called hematologic cancers, disrupt the functioning and production of blood cells. Most blood cancers begin in the bone marrow where blood is produced. In the case of leukemias, different types have been linked to various causes; however, there is still much unknown about why they occur [1–314].

Similar to other cancers, leukemia results from DNA mutation, which can activate oncogenes or deactivate tumor suppressor genes. Moreover, these genetic changes disrupt the regulation of cell death, differentiation, or division. The causal mutations may happen spontaneously or can result from exposure to radiation or carcinogenic substances. Sometimes the mutations are due to inherent genetic factors [1, 3, 7, 9, 10, 14–17, 30, 31].

Certain viruses have been linked to some types of leukemia. For instance, the human T-lymphotropic virus (HTLV-1) causes adult T-cell leukemia.

4.3 Types of Blood Cancers

The most common types of blood cancer are:

- (a) **Leukemia:** It originates in blood-forming tissue (Figures 4.1 and 4.2) [2–6].
- (b) **Non-Hodgkin’s lymphoma:** It starts in the lymphatic system with cells known as lymphocytes, a kind of white blood cell that helps the body fight infections [31–34].
- (c) **Hodgkin’s lymphoma:** It develops within the lymphatic system in the lymphocytes (Figure 4.3) and is characterized by the presence of an abnormal lymphocyte called the *Reed–Sternberg cell* (or *B lymphocyte*) [35–40].
- (d) **Multiple myeloma:** It originates in the blood’s plasma cells, a type of white blood cell made in the bone marrow that helps the body fight infection [41–47].

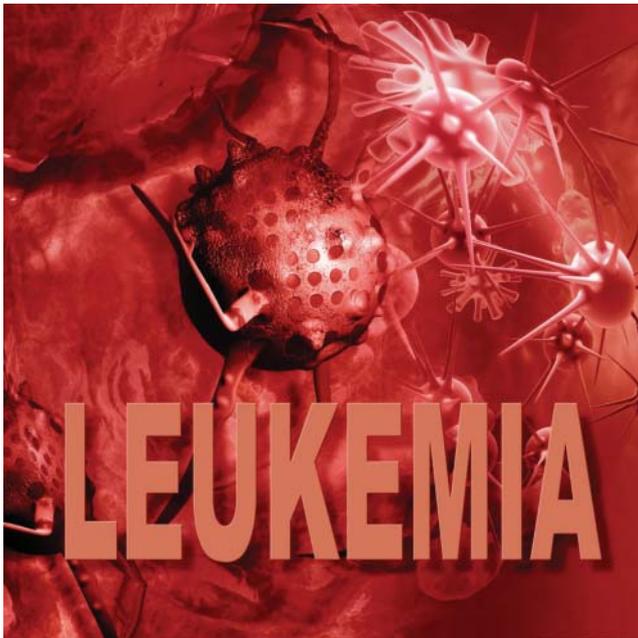


Figure 4.1 Microscopic 3-D view of cancerous white blood cells.

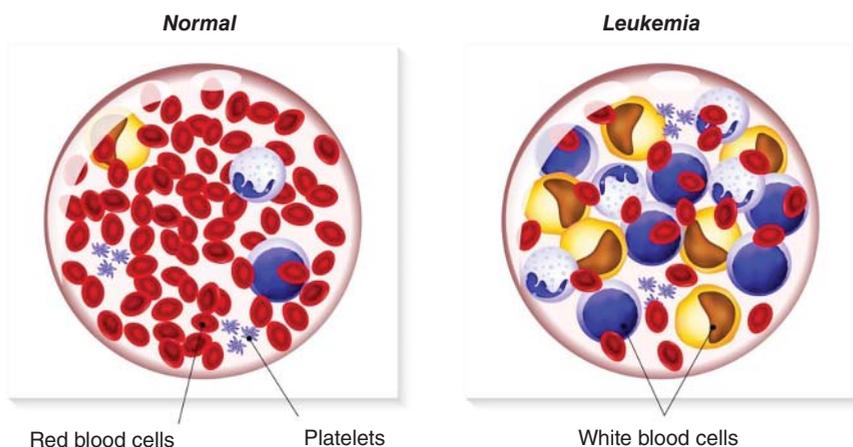


Figure 4.2 Leukemia is a type of cancer in the blood-forming tissues of the body. White blood cells are produced in excessive amounts and unable to work properly, weakening the immune system. Source: Based on [2–6].

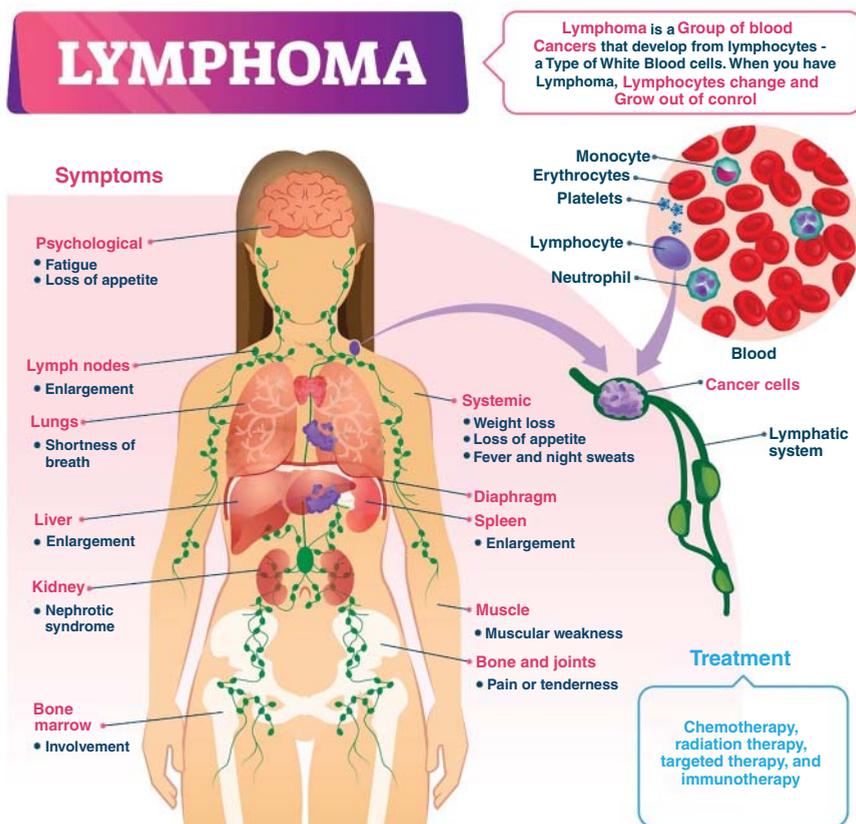


Figure 4.3 Symptoms and treatment options of lymphoma.

In adults, there are four types of leukemia. **Chronic lymphocytic leukemia (CLL)** is the most common [48–51]. **Acute lymphoblastic (or lymphocytic) leukemia (ALL)** is a type most frequently diagnosed in the 15–25 years’ age group and then in those over 75 years of age [52–56]. **Acute myeloid (or myelogenous) leukemia (AML)** is the second most common adult leukemia seen mainly in those over 60 years of age [57–61]. The rarest type is **chronic myeloid leukemia (CML)**, encountered in individuals 40–60 years of age [62–64].

4.4 Blood Cancer Symptoms

- Fever, chills
- Persistent fatigue, weakness
- Loss of appetite, nausea
- Unexplained weight loss
- Night sweat
- Bone/joint pain
- Abdominal discomfort
- Headache
- Shortness of breath
- Frequent infections
- Itchy skin or skin rash
- Swollen lymph nodes in the neck, underarms, and groin

4.5 Diagnosis

To aid diagnosis, the following tests may be performed:

- Physical examination
- Blood tests
- Complete blood counts
- Chest X-ray
- Bone marrow biopsy
- Lumbar puncture (also called a spinal tap; taking fluid from the lower back spine using a hollow needle)
- CT scan
- MRI scan
- Ultrasound scan

4.6 Methods of Treatment

The blood cancer treatment used depends on several different factors, including the type of cancer, age of the patient, how fast the cancer is progressing, and where it has spread. Below are some common blood cancer treatment regimens [1, 5, 8, 11, 12, 19, 21–370].

4.6.1 Stem Cell Transplantation

A stem cell transplant infuses healthy blood-forming stem cells into the body. Stem cells can be collected from healthy bone marrow, circulating (peripheral) blood, and umbilical cord blood.

4.6.2 Targeted Radiation Therapy

Sometimes used before or after a stem cell transplant, targeted radiation may be used to destroy cancer cells or to relieve discomfort.

4.6.3 Chemotherapy

Chemotherapy drugs can kill the cancer cells or halt their growth in the human body. Chemotherapy for blood cancer is administered using a combination of two or more drugs, and can also be given before a stem cell transplant. Some common drugs used for the treatment of blood cancer are prednisone, cyclophosphamide, etoposide, irinotecan, methotrexate, procarbazine, vincristine, fludarabine (Fludara®), pentostatin (Nipent®), cladribine (2-CdA, Leustatin®), chlorambucil (Leukeran®), bendamustine (Treanda®), cyclophosphamide (Cytosan®), and dexamethasone and nelarabine (Arranon).

4.6.4 Targeted Drug Therapy

Bevacizumab (Avastin, Mvasi, Zirabev), alemtuzumab (Campath), everolimus (Afinitor) acalabrutinib (Calquence), ibrutinib (Imbruvica), idelalisib (Zydelig), duvelisib (Copiktra), and venetoclax (Venclexta) are targeted drug therapy to treat blood cancer.

4.7 List of Drugs for Different Types of Blood Cancers

Drugs based on types of blood cancer are listed here.

4.7.1 Drugs for Acute Lymphoblastic Leukemia

Blinatumomab (Blinicyto); calaspargase pegol-mknl (Asparlas); clofarabine (Clolar); cyclophosphamide, cytarabine, and dasatinib (Sprycel); daunorubicin, dexamethasone, doxorubicin, and asparaginase *Erwinia chrysanthemi* (Erwinaze); inotuzumab ozogamicin (Besponsa); imatinib mesylate (Gleevec); mercaptopurine, methotrexate sodium, nelarabine, and pegaspargase (Oncaspar); ponatinib hydrochloride (Iclusig); prednisone and tisagenlecleucel (Kymriah); and vincristine sulfate and vincristine sulfate liposome (Marqibo).

4.7.2 Drugs for Acute Myeloid Leukemia (AML)

Arsenic trioxide, azacitidine, cyclophosphamide, cytarabine, daunorubicin hydrochloride, dexamethasone, doxorubicin hydrochloride, enasidenib mesylate,

gemtuzumab ozogamicin, gilteritinib fumarate, glasdegib maleate, idarubicin hydrochloride, ivosidenib, midostaurin, mitoxantrone hydrochloride, prednisone, thioguanine, venetoclax, and vincristine sulfate.

4.7.3 Drugs for Chronic Lymphocytic Leukemia

Acalabrutinib, alemtuzumab, bendamustine hydrochloride, chlorambucil, cyclophosphamide, dexamethasone, duvelisib, fludarabine phosphate, ibrutinib, idelalisib, obinutuzumab, ofatumumab, prednisone, rituximab and hyaluronidase human (Rituxan Hycela), rituximab, and venetoclax.

4.7.4 Drugs for Chronic Myelogenous Leukemia (CML)

Bosutinib, busulfan, cyclophosphamide, cytarabine, dasatinib, dexamethasone, hydroxyurea, imatinib mesylate, nilotinib, omacetaxine mepesuccinate, and ponatinib hydrochloride.

4.7.5 Drugs for Hairy Cell Leukemia

Cladribine, recombinant interferon alfa-2b (Intron A), and moxetumomab pasudotox-tdfk.

4.7.6 Drug(s) for Mast Cell Leukemia

Midostaurin (Rydapt).

4.7.7 Drug(s) for Meningeal Leukemia

Cytarabine.

4.7.8 Drugs for Hodgkin Lymphoma

Bleomycin sulfate, brentuximab vedotin, carmustine, chlorambucil, cyclophosphamide, dacarbazine, dexamethasone, doxorubicin hydrochloride, lomustine, nivolumab, pembrolizumab, prednisone, procarbazine hydrochloride, vinblastine sulfate, and vincristine sulfate.

4.7.9 Drugs for Non-Hodgkin Lymphoma

Acalabrutinib, axicabtagene ciloleucel, belinostat, bendamustine hydrochloride, bleomycin sulfate, bortezomib, brentuximab vedotin, brexucabtagene autoleucel, carmustine, chlorambucil, copanlisib hydrochloride, crizotinib, cyclophosphamide, denileukin diftitox, dexamethasone, doxorubicin hydrochloride, duvelisib, ibrutinib, idelalisib, lenalidomide, lisocabtagene maraleucel, loncastuximab tesirine-lpyl, methotrexate sodium,

mogamulizumab-kpkc, nelarabine, obinutuzumab, pembrolizumab, plerixafor, polatuzumab vedotin-piiq, pralatrexate, prednisone, recombinant interferon alfa-2b, rituximab, romidepsin, selinexor, tafasitamab-cxix, tazemetostat hydrobromide, tisagenlecleucel, umbralisib tosylate, venetoclax, vinblastine sulfate, vincristine sulfate, vorinostat, and zanubrutinib.

4.7.10 Drugs for Multiple Myeloma and Other Plasma Cell Neoplasms

Belantamab mafodotin-blmf, bortezomib, carfilzomib, carmustine, cyclophosphamide, daratumumab, doxorubicin hydrochloride liposome, elotuzumab, idecabtagene vicleucel, isatuximab-irfc, ixazomib citrate, lenalidomide, melphalan, pamidronate disodium, panobinostat lactate, plerixafor, pomalidomide, selinexor, thalidomide, and zoledronic acid.

4.8 Leukemia Treatment regimens

4.8.1 Treatment Regimens for Acute Lymphocytic (Lymphoblastic) Leukemia (ALL)

Generally, the four components of ALL treatment are induction, consolidation, maintenance, and the central nervous system (CNS) prophylaxis.

Linker-4 Drug Regimens

Induction Therapy

Daunorubicin: 50 mg/m² IV daily on days 1–3
 Vincristine: 2 mg IV on days 1, 8, 15, and 22
 Prednisone: 60 mg/m² orally on days 1–28
 L-Asparaginase: 6000 IU/m² IM on days 17–28
 If bone marrow on day 14 remains residual leukemia
 Daunorubicin: 50 mg/m² IV on day 15
 If bone marrow on day 28 remains residual leukemia
 Daunorubicin: 50 mg/m² IV on days 29 and 30
 L-asparaginase: 6000 IU/m²/day IM on days 29–35
 Prednisone: 60 mg/m²/day orally on days 29–42

Consolidation Therapy

Treatment A: Cycles 1, 3, 5, and 7

Daunorubicin: 50 mg/m² IV on days 1 and 2
 Vincristine: 2 mg IV on days 1 and 8
 Prednisone: 60 mg/m² orally on days 1–14
 L-Asparaginase: 12000 IU/m² IM on days 2, 4, 7, 9, 11, and 14

Treatment B: Cycles 2, 4, 6, and 8

Teniposide: 165 mg/m² IV on days 1, 4, 8, and 11
 Cytarabine: 300 mg/m² IV on days 1, 4, 8, and 11

Treatment C: Cycle 9

Methotrexate: 690 mg/m² IV over 42 hours
 Leucovorin: 15 mg/m² IV every six hours for 12 doses starting at 42 hours

Maintenance Therapy**Linker-4 Drug Regimens**

Methotrexate: 20 mg/m² orally weekly
 6-Mercaptopurine: 75 mg/m² orally once daily
 Continue treatment for a total of 30 months [70–72].

CNS Prophylaxis

Cranial irradiation: 1800 cGy in 10 fractions over 12–14 days
 Methotrexate: 12 mg IT weekly for six weeks

Larson 5-drug Regimen (CALGB 8811 regimen)**Induction therapy** (weeks 1–4)

Cyclophosphamide: 1200 mg/m² IV on day 1
 Daunorubicin: 45 mg/m² IV on days 1–3
 Vincristine: 2 mg IV on days 1, 8, 15, and 22
 Prednisone: 60 mg/m²/day orally on days 1–21
 L-Asparaginase: 6000 IU/m² SC on days 5, 8, 11, 15, 18, and 22

Consolidation Therapy (early intensification weeks 5–12)

Methotrexate: 15 mg IT on day 1
 Cyclophosphamide: 1000 mg/m² IV on day 1
 6-Mercaptopurine: 60 mg/m²/day orally on days 1–14
 Cytarabine: 75 mg/m² IV on days 1–4 and 8–11
 Vincristine: 2 mg IV on days 15 and 22
 L-Asparaginase: 6000 IU/m² SC on days 15, 18, 22, and 25
 Repeat this cycle once.

Interim Maintenance and CNS Prophylaxis (weeks 13–25)

Cranial irradiation: 2400 cGy on days 1–12
 Methotrexate: 15 mg IT on days 1, 8, 15, 22, and 29
 6-Mercaptopurine: 60 mg/m²/day orally on days 1–70
 Methotrexate: 20 mg/m² orally on days 36, 43, 50, 57, and 64, followed by:

Late Intensification (weeks 26–33)

Doxorubicin: 30 mg/m² IV on days 1, 8, and 15
 Vincristine: 2 mg IV on days 1, 8, and 15
 Dexamethasone: 10 mg/m²/day orally on days 1–14
 Cyclophosphamide: 1000 mg/m² IV on day 29
 6-Thioguanine: 60 mg/m²/day orally on days 29–42
 Cytarabine: 75 mg/m² IV on days 29, 32, and 36–39, followed by:

Prolonged Maintenance

Vincristine: 2 mg IV on day 1
 Prednisone: 60 mg/m²/day orally on days 1–5
 Methotrexate: 20 mg/m² orally on days 1, 8, 15, and 22
 6-Mercaptopurine: 80 mg/m²/day orally on days 1–28
 Repeat maintenance cycle every four weeks until 24 months from diagnosis [73].

Hyper-CVAD ± Rituximab Regimen

Cyclophosphamide: 300 mg/m² IV infusion over three hours every 12 hours for six doses on days 1–3
 Mesna: 600 mg/m²/day IV continuous infusion on days 1–3, starting with cyclophosphamide and finishing 12 hours after the last dose of cyclophosphamide
 Vincristine: 2 mg IV on days 4 and 11
 Doxorubicin: 50 mg/m² IV infusion over two hours on day 4
 Dexamethasone: 40 mg IV or PO on days 1–4 and 11–14
 Alternate cycles every 21 days with the following:
 Methotrexate: 200 mg/m² IV over two hours, followed by 800 mg/m² IV over 24 hours on day 1
 Leucovorin: 15 mg IV every six hours for eight doses, starting 24 hours after the completion of methotrexate
 Methylprednisolone: 50 mg IV twice daily on days 1–3
 Alternate four cycles of hyper-CVAD with four cycles of high-dose methotrexate and cytarabine [74, 75] as follows:
 Cytarabine: 3 g/m² IV (1 g/m² patients > 60 years old) infusion over two hours every 12 hours on days 2–3±
 Rituximab: 375 mg/m² IV on days 1 and 8

CNS Prophylaxis

Methotrexate: 12 mg IT on day 2
 Cytarabine: 100 mg IT on day 8

Clofarabine + Etoposide + Cyclophosphamide

Clofarabine: 40 mg/m² IV daily on days 1–5
 Etoposide: 100 mg/m² IV daily on days 1–5
 Cyclophosphamide: 440 mg/m² IV daily on days 1–5
 Continue 1 or 2 induction cycles (five days' chemotherapy) and followed by 1–3 consolidation cycles (four days of chemotherapy) for a maximum of five cycles [314].

Single-Agent Regimens**Blinatumomab**

Cycle 1
 9 µg/day IV continuous infusion on days 1–7
 28 µg/day IV continuous infusion on days 8–28

Subsequent cycles

28 $\mu\text{g}/\text{day}$ IV continuous infusion on days 1–28

Repeat cycle every 42 days [76–78].

Clofarabine

52 mg/m^2 IV on days 1–5

Repeat cycle every 2–6 weeks [79].

Dasatinib (Philadelphia chromosome-positive ALL)

70 mg orally twice daily or 140 mg orally once daily

Continue until disease progression or unacceptable toxicity [80–82].

Imatinib (for Ph + ALL)

600 mg orally once daily

Continue until disease progression or unacceptable toxicity [83].

Intuzumab

0.8 mg/m^2 IV on days 1, 8, and 15

Repeat cycle every 21 days [84].

Nelarabine (for Ph + ALL)

1.5 $\text{g}/\text{m}^2/\text{day}$ IV over two hours on days 1, 3, and 5

Repeat cycle every 21 days [85].

Nilotinib (for Ph + ALL)

400–600 mg orally twice daily

Continue until disease progression or unacceptable toxicity [86].

Ponatinib (for Ph + ALL)

45 mg orally once daily

Continue until disease progression or unacceptable toxicity [87].

Liposomal Vincristine Sulfate

2.25 mg/m^2 IV over one hour once weekly

Continue until disease progression or unacceptable toxicity [88, 89].

4.8.2 Acute Myeloid (or Myelogenous) Leukemia (AML) Treatment Regimens

Induction Therapy

Cytarabine + Daunorubicin [91]

Cytarabine: 100 $\text{mg}/\text{m}^2/\text{day}$ IV continuous infusion on days 1–7

Daunorubicin: 45 mg/m^2 IV on days 1–3

Dual-Drug Liposomal Encapsulation of Cytarabine and Daunorubicin

Liposomal daunorubicin 100 U/m² IV infusion over 90 minutes on days 1, 3, and 5 (delivering 100 mg/m² cytarabine and 44 mg/m² daunorubicin with each dose)

Second induction and consolidation courses: 100 U/m² on days 1 and 3

Continue as many as two courses of induction and two courses of consolidation therapy [92].

Cytarabine + Daunorubicin + Gemtuzumab Ozogamicin

Cytarabine: 200 mg/m² IV continuous infusion on days 1–7

Daunorubicin: 60 mg/m² IV on days 1–3

Gemtuzumab ozogamicin: 3 mg/m² IV on days 1, 4, and 7

Patients in remission following induction therapy, then they can receive two cycles of consolidation therapy using the above-mentioned cytarabine and daunorubicin doses but gemtuzumab ozogamicin dose is 3 mg/m² on day 1 only [93, 97].

Cytarabine + Idarubicin [94]

Cytarabine: 100 mg/m² IV continuous infusion on days 1–7

Idarubicin: 12 mg/m² IV on days 1–3

Cytarabine + Clofarabine

Cytarabine: 1 g/m² IV infusion over two hours on days 1–5

Clofarabine: 40 mg/m² IV infusion over one hour on days 2–6

Patients who achieve remission after their induction cycle should receive a single (optional) consolidation cycle [95].

Cytarabine + Daunorubicin + Midostaurin

Cytarabine: 200 mg/m² IV continuous infusion on days 1–7

Daunorubicin: 60 mg/m² IV on days 1–3

Midostaurin: 50 mg/m² orally twice daily on days 8–21

If there is evidence of clinically significant residual leukemia, a second cycle of induction therapy that is identical to the first can be repeated [96].

Post-Remission Therapy Regimens**Cytarabine + Daunorubicin**

Cytarabine: 100 mg/m² IV continuous infusion on days 1–5

Daunorubicin: 45 mg/m² IV on days 1 and 2

Dual-Drug Liposomal Encapsulation of Cytarabine and Daunorubicin

CPX-351: 65 units/m² (daunorubicin 29 mg/m² and cytarabine 65 mg/m²) IV on days 1 and 3

Continue 5–6 cycles [100].

High-Dose Cytarabine

3 g/m² IV infusion over three hours in every 12 hours on days 1, 3, and 5
Repeat cycle every 28 days for four cycles.

Or

Cytarabine

3 g/m² IV infusion over three hours every 12 hours on days 1, 3, and 5 for two cycles
plus autologous stem cell transplantation [103].

Cytarabine + Idarubicin

Cytarabine: 100 mg/m² IV continuous infusion on days 1–5

Idarubicin: 13 mg/m² IV on days 1 and 2

Repeat cycle every 21 days.

Cytarabine + Midostaurin

Cytarabine: 3 g/m² IV infusion over three hours in every 12 hours on
days 1, 3, and 5

Midostaurin: 50 mg orally twice daily on days 8–21

Repeat cycle every four weeks for four cycles [96].

Regimens for Relapsed or Refractory Disease**Etoposide + Cytarabine + Mitoxantrone [105]**

Etoposide: 80 mg/m² IV over one hour on days 1–6

Cytarabine: 1 g/m² IV over six hours on days 1–6

Mitoxantrone: 6 mg/m² IV bolus on days 1–6

Cladribine + Cytarabine + Mitoxantrone + Filgrastim [106]

Cladribine: 5 mg/m² IV over two hours daily on days 1–5

Cytarabine: 2 g/m² IV over four hours daily on days 1–5

Mitoxantrone: 10 mg/m² IV daily on days 1–3

Filgrastim: 300 µg daily starting 24 hours prior to chemotherapy and on
days 1–5

Glasdegib + Cytarabine

Glasdegib: 100 mg orally once daily on days 1–28

Cytarabine: 20 mg SC twice daily on days 1–10

Repeat cycle every 28 days for a total of six cycles [107].

Venetoclax + Azacitidine (for isocitrate dehydrogenase 2 (IDH2) mutation)

Venetoclax: 100 mg orally once on day 1, 200 mg on day 2, 300 mg on day
3; day 4 and beyond 400 mg orally once daily

Azacitidine: 75 mg/m² IV on days 1–7

Repeat cycle every 28 days and continue until disease progression or unacceptable
toxicity [108].

Venetoclax + Decitabine

Venetoclax: 100 mg orally once on day 1, 200 mg on day 2, 300 mg on day 3; day 4 and beyond 400 mg orally once daily

Decitabine: 20 mg/m² IV on days 1–5

Repeat cycle every 28 days and continue until disease progression or unacceptable toxicity [108].

Azacitidine + Sorafenib [for *FLT3* mutation]

Azacitidine: 75 mg/m² IV daily on days 1–7

Sorafenib: 400 mg orally twice daily on days 1–7

Repeat cycles at 1-month intervals [116].

Single-Agent Regimens for AML**Enasidenib (for *IDH-2* positive AML)**

100 mg orally once daily with or without food

Continue until disease progression or unacceptable toxicity [109].

Ivosidenib (*IDH1*-mutated relapsed or refractory AML)

500 mg orally once daily with or without food

Continue until disease progression or unacceptable toxicity [110].

Gilteritinib (*FLT3*-positive AML)

120 mg orally once daily

Repeat cycle every 28 days for at least six months for clinical response or until disease progression or unacceptable toxicity [317].

Azacitidine

75 mg/m² IV or SC daily for seven days

Repeat cycle every 28 days [111].

Gemtuzumab ozogamicin (*CD33*-positive AML)

3 mg/m² IV infusion over two hours on days 1, 4, and 7

Repeat as one induction therapy and one consolidation therapy [316].

Arsenic trioxide (for acute promyelocytic leukemia only)

0.15 mg/kg IV infusion over one hour five days per week

Continue five weeks with a two-week interval between courses [112].

Clofarabine

30 mg/m² IV infusion over one hour on days 1–5 during induction and 20 mg/m² IV infusion over one hour on days 1–5 during consolidation

Continue for a maximum of six cycles [113].

Sorafenib (for *FLT3* mutated AML)

200–400 mg orally twice daily

Continue until disease progression [117].

Decitabine

20 mg/m² IV infusion over one hour on days 1–5
Repeat cycle every four weeks [118].

4.8.3 Chronic Lymphocytic Leukemia Treatment Regimens**Single-Agent Regimens****Acalabrutinib**

100 mg orally once daily
Continue until disease progression or unacceptable toxicity [119, 121].

Alemtuzumab

30 mg/day IV infusion over two hours three times per week on alternate days
Repeat cycle every week for a total of 23 cycles [120]

Bendamustine

100 mg/m² IV infusion over 30 minutes on days 1 and 2
Repeat cycle every 28 days for six cycles [122].

Chlorambucil

0.4 mg/kg/day with an increase to 0.8 mg/kg orally daily on days 1–28
Repeat cycle every 28 days for 12 cycles [119–124].

Duvelisib

25 mg orally twice daily
Repeat cycle every 28 days [125].

Fludarabine

20–30 mg/m² IV infusion over a period of 10–30 minutes on days 1–5
Repeat cycle every 28 days [123].

Ibrutinib

420 mg orally once daily
Continue until disease progression or unacceptable toxicity [126].

Lenalidomide

10 mg orally daily (start at 2.5 mg/day and escalate as tolerated up to 25 mg/day)
Continue until disease progression or unacceptable toxicity [127].

Ofatumumab

300 mg IV on day 1 followed by 1000 mg one week later and every eight weeks for up to two years [128].

Rituximab

375 mg/m²/day IV weekly, start at 50 mg/hour during the first hour and increase to final 400 mg/hour if well tolerated.
Repeat cycle every four weeks for six cycles [129].

Venetoclax

A weekly ramp-up schedule starting at 20 mg orally once daily and increasing to 50, 100, 200 mg, and, finally, 400 mg once daily.

Continue until disease progression or unacceptable toxicity [130].

Obinutuzumab

Cycle 1

100 mg IV on day 1

900 mg IV on day 2

1000 mg IV on day 3

2000 mg IV on days 8 and 15

Cycles 2–8

2000 mg IV on day 1

Repeat cycle every 21 days [131].

Cladribine

0.12 mg/kg/day IV infusion over two hours on days 1–5

Repeat cycle every 28 days for six cycles [318].

Combination Regimens**Bendamustine + Rituximab**

Bendamustine: 90 mg/m² IV on days 1 and 2

Rituximab: 375 mg/m² IV on day 0 of cycle 1, then 500 mg/m² IV on day 1 for all subsequent cycles (cycles 2–6)

Repeat cycle every 28 days for six cycles [132].

Obinutuzumab + Chlorambucil

Obinutuzumab: 100 mg IV on day 1

900 mg IV on day 2

1000 mg IV on days 8 and 15

1000 mg IV on day 1 of all subsequent cycles (from cycle 2–6)

Chlorambucil: 0.5 mg/kg orally once on days 1 and 15

Repeat cycle every 28 days [133].

Ofatumumab + Chlorambucil

Cycle 1

Ofatumumab: 300 mg IV on day 1 and 1000 mg IV on day 8

Chlorambucil: 10 mg/m² orally on days 1–7

Subsequent cycles

Ofatumumab: 1000 mg IV on day 1

Chlorambucil: 10 mg/m² orally on days 1–7

Repeat cycle every 28 days for a total of 12 cycles [134].

Chlorambucil + Prednisone

Chlorambucil: 30 mg/m² orally on day 1

Prednisone: 80 mg orally on days 1–5

Repeat cycle every 28 days [135].

Chlorambucil + Rituximab

Chlorambucil: 10 mg/m²/day orally on days 1–7 of each cycle
 Rituximab: 375 mg/m² IV on day 1 of cycle 1, then increase to
 500 mg/m² IV on day 1 of cycles 2 to 6
 Repeat cycle every 28 days for six cycles [136].

Cyclophosphamide + Fludarabine

Cyclophosphamide: 600 mg/m² IV over one hour on day 1
 Fludarabine: 20 mg/m² IV over 30 minutes on days 1–5
 Repeat cycle every 28 days for a total of six cycles [319].

Fludarabine + Rituximab

Fludarabine: 25 mg/m² IV over 30 minutes on days 1–5
 Rituximab: 375 mg/m² IV on days 1 and 4 of cycle 1, and then
 375 mg/m² IV on day 1 of each cycle
 Repeat cycle every 28 days for a total of six cycles [138].

Idelalisib + Rituximab

Idelalisib: 150 mg orally twice daily
 Rituximab: 375 mg/m² IV on day 1, then 500 mg/m² IV every two weeks for four
 doses and then every four weeks for three doses, for a maximum of
 eight doses [139].

Ibrutinib + Rituximab

Ibrutinib: 420 mg orally once daily on days 1–28
 Rituximab: 50 mg/m² IV on day 1 of cycle 2
 325 mg/m² on day 2 of cycle 2
 500 mg/m² IV on day 1 of cycles 3–7
 Repeat cycle every four weeks [140].

Venetoclax + Rituximab

Venetoclax: 20 mg orally once daily on days 1–7
 50 mg orally once daily on days 8–14
 100 mg orally once daily on days 15–21
 200 mg orally once daily on days 22–28, then
 400 mg orally once daily
 Rituximab: After completion of the dose ramp-up period for venetoclax
 up to 400 mg/day, this will be day 1 of cycle 1, Rituximab
 dose is 375 mg/m² IV on day 1 of cycle 1, followed by
 500 mg/m² IV on day 1 of cycles 2–6
 Repeat cycle every 28 days for six cycles [141]. After cycle 6, administration of
 venetoclax at a dose of 400 mg per day is continued for two years.

Venetoclax + Obinutuzumab

Obinutuzumab: 100 mg IV on day 1, 900 mg IV on day 2 (or 1000 mg IV on day 1), 1000 mg on day 8, and 1000 mg on day 15 of cycle 1, and, subsequently, 1000 mg on day 1 of cycles 2 through 6.

Venetoclax: Begin on day 22 of cycle 1 with a five-week dose ramp-up schedule (one week each of 20, 50, 100, and 200 mg orally, then 400 mg orally daily for one week), continue 400 mg orally daily up to cycle 12

Repeat cycle every 28 days for up to six cycles with Obinutuzumab and 12 cycles with venetoclax [320].

CVP

Cyclophosphamide: 400 mg/m² orally on days 1–5

Vincristine: 1.4 mg/m² IV on day 1

Prednisone: 100 mg/m² orally on days 1–5

Repeat cycle every 21 days and continue for up to 18 months to maximal response [135].

FCR

Fludarabine: 25 mg/m² IV on days 1–3

Cyclophosphamide: 250 mg/m² IV on days 1–3

Rituximab: 375 mg/m² IV on day 1 of cycle 1 and 500 mg/m² IV on day 1 of cycles 2–6

Repeat cycle every four weeks for six cycles [137, 142].

PCR

Pentostatin: 2 mg/m² IV on days 1 and 2

Cyclophosphamide: 600 mg/m² IV over 15–60 minutes on day 1

Rituximab: 375 mg/m² IV on day 1

Repeat cycle every 21 days for six cycles [143].

4.8.4 Chronic Myeloid Leukemia (CML) Treatment Regimens**Single-Agent Regimens****Bosutinib**

400–500 mg orally once daily with food

Continue until disease progression or unacceptable toxicity [145, 146].

Dasatinib

70 mg orally twice daily [149].

Imatinib

400 mg orally once daily for chronic phase and 600 mg orally once daily for accelerated phase [147–149].

Nilotinib

300–400 mg orally twice daily

Continue until disease progression or unacceptable toxicity occurs [150, 151].

Omacetaxine

1.25 mg/m² SC twice daily on days 1–14 until hematologic response or a maximum of six cycles, and then days 1–7 every 28 days as the maintenance phase.

Repeat cycle every 28 days until disease progression or unacceptable toxicity [152].

Ponatinib

45 mg orally twice daily

Continue until disease progression [153].

Asciminib

20–200 mg orally once or twice daily

Continue until disease progression [321].

Radotinib

300 mg orally twice daily

Continue until disease progression or unacceptable toxicity occurs [322].

Danusertib

180 mg/m² IV infusion over three hours on days 1–7

Repeat cycle every 14 days (7 days on/7 days off) [325].

Tozasertib

24–40 mg/m²/hour IV continuous five days

Repeat cycle every 14 days [326].

Ruxolitinib + Nilotinib

Ruxolitinib: 5, 10, and 15 mg orally twice daily

Nilotinib: 300–400 mg orally twice daily

Continue for six months [327].

Lonafarnib + Imatinib

Lonafarnib: 100 mg orally twice daily

Imatinib: 400 mg orally once daily.

Continue until disease progression or unacceptable toxicity occurs [323].

Tipifarnib + Imatinib

Tipifarnib: 300 mg orally twice daily on days 1–14 (14 days on/7 days off)

Imatinib: 300 mg orally once daily on days 1–21

Repeat cycle every 21 days [324].

Interferon α -2a + Cytarabine

Interferon α -2a: 5 million IU/m² SC daily on days 1–28

Cytarabine: 20 mg/m² SC (maximum 40 mg) daily for 10 days every 28 days

Repeat cycle every 28 days [154].

4.8.5 Hairy Cell Leukemia Treatment Regimens

Cladribine

0.09 mg/kg/day IV continuous infusion on days 1–7
One cycle only [155].

Interferon α -2b

3 million U/m² SC 3 times per week
Continue for 12–18 months for relapsed or refractory HCL [156].

Pentostatin

4 mg/m² IV over 30 minutes with 1.5 L hydration
Repeat cycle every two weeks for 6–12 cycles [157].

Moxetumomab pasudotox-tdfk

0.04 mg/kg IV over 30 minutes on days 1, 3, and 5
Repeat cycle every 28 days for a total of six cycles [158].

Vemurafenib + Rituximab

Vemurafenib: 960 mg orally twice daily on days 1–28
Rituximab: 375 mg/m² IV on days 1 and 15
Repeat cycle every 28 days [328].

4.9 Hodgkin's Lymphoma Treatment Regimens

Single-Agent Regimens

Bendamustine

120 mg/m² IV over 30 minutes on days 1 and 2
Repeat cycle every four weeks until maximal response or unacceptable toxicity [159].
Administer growth factor support with pegfilgrastim or filgrastim with each cycle of treatment.

Brentuximab Vedotin

1.8 mg/kg IV over 30 minutes on day 1
Repeat cycle every three weeks and continue until disease progression or unacceptable toxicity occurs [160, 161].

Everolimus

10 mg orally once daily
Continue until disease progression or unacceptable toxicity occurs [162].

Gemcitabine

1000 mg/m² IV over 30 minutes on days 1 and 15
Repeat cycle every 28 days [329].

Lenalidomide

25 mg orally once daily on days 1–21
Repeat cycle every four weeks (3 weeks on/1 week off) until disease progression or an unacceptable adverse event occurs [163].

Nivolumab

3 mg/kg IV every two weeks

Repeat cycle every two weeks until disease progression or unacceptable toxicity [164, 165].

Pembrolizumab

10 mg/kg IV every two weeks

Continue until disease progression or unacceptable toxicity [166].

Rituximab

375 mg/m² IV on day 1

Repeat cycle every seven days for four weeks with or without maintenance rituximab (375 mg/m² IV once weekly for four weeks every six months for up to two years) [167–171].

Combination Regimens**Doxorubicin + Bleomycin + Vinblastine + Dacarbazine (ABVD)**

Doxorubicin: 25 mg/m² IV on days 1 and 15

Bleomycin: 10 U/m² IV on days 1 and 15

Vinblastine: 6 mg/m² IV over 5–10 minutes on days 1 and 15

Dacarbazine: 375 mg/m² IV over 60 minutes on days 1 and 15

Repeat cycle every 28 days with involved-site radiation therapy (ISRT) or without radiation therapy [172–175].

Brentuximab + Doxorubicin + Vinblastine + Dacarbazine

Brentuximab vedotin: 1.2 mg/kg IV on days 1 and 15

Doxorubicin: 25 mg/m² IV on days 1 and 15

Vinblastine: 6 mg/m² IV over 5–10 minutes on days 1 and 15

Dacarbazine: 375 mg/m² IV over 60 minutes on days 1 and 15

Repeat cycle every 28 days [330].

MOPP

(**M**)ustargen (also known as mechlorethamine, chlormethine, mustine, nitrogen mustard, or MSD)

(**O**)ncovin (also known as Vincristine or VCR)

(**P**)rocarbazine (also known as Matulane or Natulan)

(**P**)rednisone

Nitrogen mustard: 6 mg/m² IV bolus on days 1 and 8

Vincristine: 1.4 mg/m² IV bolus (maximum 2 mg) on days 1 and 8

Procarbazine: 100 mg/m² orally once daily on days 1–14

Prednisone: 40 mg/m² orally once daily on days 1–14

Repeat cycle every 28 days [180].

C-MOPP

Cyclophosphamide: 650 mg/m² IV infusion over 30 minutes on day 1
 Vincristine: 1.4 mg/m² IV bolus (not to exceed 2 mg/dose) on day 1
 Procarbazine: 100 mg/m² orally once daily on days 1–7
 Prednisone: 40 mg/m² orally once daily on days 1–14
 Repeat cycle every 28 days [331].

Stanford V

Mechlorethamine: 6 mg/m² IV on day 1
 Doxorubicin: 25 mg/m² IV on days 1 and 15
 Vinblastine: 6 mg/m² IV over 5–10 minutes on days 1 and 15
 Vincristine: 1.4 mg/m² IV (not to exceed 2 mg/dose) bolus on days 8 and 22
 Bleomycin: 5 U/m² IV on days 8 and 22
 Etoposide: 60 mg/m² IV over 60 minutes on days 15 and 16
 Prednisone: 40 mg/m² orally every other day and Taper prednisone dose by 10 mg every other day beginning day 15 of cycle 2.
 Repeat cycle every 28 days with ISRT 36 Gy [176–179].

EVAP

Etoposide: 120 mg/m² IV over 60 minutes on days 1, 8, and 15
 Vinblastine: 4 mg/m² IV over 5–10 minutes on days 1, 8, and 15
 Cytarabine: 30 mg/m² IV on days 1, 8, and 15
 Cisplatin: 40 mg/m² IV on days 1, 8, and 15
 Repeat cycle every four weeks for six cycles [180].

Carmustine + Cytarabine + Etoposide + Melphalan (Mini-BEAM)

Carmustine: 60 mg/m² IV on day 1
 Etoposide: 75 mg/m² IV on days 2–5
 Cytarabine: 100 mg IV every 12 hours on days 2–5
 Melphalan: 30 mg/m² IV on day 6
 Repeat cycle every 4–6 weeks for 2–4 cycles [181, 182].

GVD**Gemcitabine + Vinorelbine + Pegylated liposomal doxorubicin (Doxil)**

For transplant-naïve patients:

Vinorelbine: 20 mg/m² IV over 6–10 minutes on days 1 and 8, give first
 Gemcitabine: 1000 mg/m² IV over 30 minutes on days 1, 8, and 15, give second
 Doxil: 15 mg/m² IV over 30–60 minutes on days 1 and 8
 Repeat cycle every three weeks for 2–4 cycles (transplant candidates) or 4–8 cycles (nontransplant candidates)

For post-transplant patients:

Vinorelbine: 15 mg/m² IV over 6–10 minutes on days 1 and 8, give first
 Gemcitabine: 800 mg/m² IV over 30 minutes on days 1, 8, and 15, give second
 Doxil: 10 mg/m² IV over 30–60 minutes on days 1 and 8
 Repeat cycle every three weeks for 2–4 cycles (transplant candidates) or 4–8 cycles (nontransplant candidates) [183].

Cyclophosphamide + Vincristine + Prednisone (CVP)

Cyclophosphamide: 500 mg/m² on day 1
 Vincristine: 1.4 mg/m² IV over 6–10 minutes on days 1 and 8
 Prednisone: 40 mg orally daily on days 1–7
 Repeat cycle at 2–3 weeks' interval [184].

Cyclophosphamide + Doxorubicin + Vincristine + Prednisone (CHOP) ± Rituximab

Cyclophosphamide: 750 mg/m² on day 1
 Doxorubicin: 50 mg/m² IV on day 1
 Vincristine: 1.4 mg/m² IV over 6–10 minutes on days 1 and 8
 Prednisone: 100 mg orally daily on days 1–5 ±
 Rituximab: 375 mg/m² IV on day 1
 Repeat cycle every 21 days with radiation therapy or without radiation therapy [334, 335].

Gemcitabine + Carboplatin + Dexamethasone ± Rituximab

Gemcitabine: 1000 mg/m² IV over 30 minutes on days 1 and 8
 Carboplatin: AUC of 5, IV over 30 minutes on day 1
 Dexamethasone: 40 mg orally daily on days 1–4 ± Rituximab
 Rituximab: 375 mg/m² IV slow infusion on day 8
 Repeat cycle every three weeks [186].

Dexamethasone + Cytarabine + Cisplatin (DHAP)

Dexamethasone: 40 mg orally daily on days 1–4
 Cisplatin: 100 mg/m² IV continuous infusion over 24 hours on day 1
 Cytarabine: 2000 mg IV over three hours once every 12 hours on day 2
 Repeat cycle every 3–4 weeks for 2–4 cycles [187, 188].

BEACOPP

Bleomycin: 10 U/m² IV on day 8
 Etoposide: 100 mg/m² IV over 60 minutes on days 1–3
 Doxorubicin: 25 mg/m² IV over 10 minutes on day 1
 Cyclophosphamide: 650 mg/m² IV over 60 minutes on day 1
 Vincristine: 1.4 mg/m² IV over 6–10 minutes on day 8 (not to exceed 2 mg/dose)
 Procarbazine 100 mg/m² orally on days 1–7
 Prednisone: 40 mg/m² orally daily on days 1–14
 Repeat cycle every 21 days [332].

Escalated BEACOPP

Bleomycin: 10 U/m² IV on day 8
 Etoposide: 200 mg/m² IV over 60 minutes on days 1–3
 Doxorubicin: 35 mg/m² IV over 10 minutes on day 1
 Cyclophosphamide: 1250 mg/m² IV over 60 minutes on day 1
 Vincristine: 1.4 mg/m² IV over 6–10 minutes on day 1
 Procarbazine 100 mg/m² orally on days 1–7
 Prednisone: 40 mg/m² orally daily on days 1–14
 Repeat cycle every 21 days [190].

Mitoxantrone + Ifosfamide + Mesna + Etoposide (MINE)

Mesna: 1.33 g/m² IV daily on days 1–3 and 500 mg orally daily four hours after each IV dose
 Ifosfamide: 1.33 g/m² IV daily on days 1–3, give concurrently with mesna
 Mitoxantrone: 8 mg/m² IV on day 1
 Etoposide: 65 mg/m² IV daily on days 1–3
 Repeat cycle every 21–28 days [333].

Ifosfamide + Carboplatin + Etoposide

Etoposide: 100 mg/m² IV daily on days 1–3
 Carboplatin: AUC of 5, IV over 30 minutes on day 2
 Ifosfamide: 5 gm/m² mixed with an equal dose of MESNA, IV continuous infusion over 24 hours on day 2
 Repeat cycle with a 2-week interval [336].

4.10 Non-Hodgkin's Lymphoma Treatment Regimens

The treatment of non-Hodgkin's lymphoma (NHL) depends on the following factors:

- Tumor stage, phenotype (B-cell, T-cell or natural killer [NK] cell/null-cell),
- histology (i.e. low, intermediate, or high-grade), symptoms, performance status, patient age, comorbidities, and others.

Single-Agent Regimens**Bendamustine**

120 mg/m² IV infusion over 30 minutes on days 1 and 2
 Repeat cycle every 21 days for six cycles [192].

Belinostat (Peripheral T-Cell Lymphoma)

1000 mg/m² IV over 30 minutes on days 1–5
 Repeat cycle every 21 days until disease progression or unacceptable toxicity or hematopoietic stem-cell transplantation (HSCT), loss to follow-up, or patient or investigator decision [193].

Brentuximab Vedotin

1.8 mg/kg IV on day 1

Repeat every cycle 21 days for 16 cycles [194].

Bortezomib (Mantle Cell Lymphoma/Peripheral T-Cell Lymphoma)

1.3 mg/m² IV on days 1, 4, 8, and 11

Repeat cycle every three weeks for up to 16 cycles [195].

Ibrutinib

560 mg orally once daily on days 1–28

Repeat cycle every four weeks until disease progression or unacceptable levels of toxicity occurs [197].

Lenalidomide

25 mg orally daily on days 1–21

Repeat cycle every four weeks (3 weeks on/1 week off) for 24 months [198].

Rituximab

375 mg/m² IV on days 1, 8, 15, and 22

Repeat one additional cycle [200].

Romidespin (Peripheral T-Cell Lymphoma)

14 mg/m² IV infusion over four hours on days 1, 8, and 15

Repeat cycle every 28 days for six cycles [201, 337].

Pralatrexate (Peripheral T-Cell Lymphoma)

30 mg/m² IV infusion over 3–5 minutes weekly for six weeks

Repeat cycle every seven weeks until progressive disease (PD), unacceptable toxicity, or patient/physician discretion. A dose omission or reduction to 20 mg/m²/week was permitted on meeting prespecified safety criteria [338].

Vorinostat (Peripheral T-Cell Lymphoma)

400 mg orally once daily, the dose can be reduced for toxicity to 300 mg daily or 300 mg five days a week.

Continue until disease progression or unacceptable toxicity occurs [202].

Acalabrutinib (Mantle Cell Lymphoma)

100 mg orally twice daily every 12 hours swallow whole with water and with or without food

Continue until disease progression or unacceptable toxicity [203].

Cyclosporine (Peripheral T-Cell Lymphoma)

3–5 mg/kg orally twice daily

Repeat cycle every 6–8 weeks with dose increasing to 50 mg every 1–3 weeks [339].

Zanubrutinib (Mantle Cell Lymphoma)

160 mg orally twice daily or 320 mg orally once daily swallow whole with water and with or without food.

Continue until disease progression or unacceptable toxicity [204].

Copanlisib

60 mg IV on days 1, 8, and 15

Repeat cycle every 28 days and continue until disease progression or unacceptable toxicity [205].

Duvelisib

25 mg orally twice daily with or without food

Repeat cycle every 28 days until progression or unacceptable toxicity occurs [206].

Umbralisib

800 mg or 1200 mg orally once daily

Continue until disease progression or unacceptable toxicity [207].

Axicabtagene Ciloleucel

2×10^6 anti-CD19 CAR-positive viable T cells/kg, with a maximum of 2×10^8 CAR-positive viable T cells IV infusion [208].

Tazemetostat

Start from 100 mg orally twice daily to 1600 mg orally twice daily with or without food

Repeat cycle every 28 days and continue until disease progression or unacceptable toxicity [209].

Tisagenlecleucel

Administer 1.00×10^8 to 5.00×10^8 CAR-positive viable T cells [210].

Alemtuzumab (Anti-CD52 Monoclonal Antibody for Peripheral T-Cell Lymphoma)

3 mg on day 1, 10 mg on day 3, followed by 30 mg, three times a week, for a maximum of 12 weeks [340].

Gemcitabine (for Peripheral T-Cell Lymphoma)

1200 mg/m² IV infusion over 30 minutes on days 1, 8, and 15

Repeat cycle every 28 days for three cycles [341].

Selinexor

60 mg orally once daily on days 1 and 3

Repeat cycle weekly until disease progression or unacceptable toxicity [353].

Combination Regimens

Regimens may vary depending on low-grade, intermediate-grade, and high-grade lymphomas.

Bendamustine + Obinutuzumab

Bendamustine: 90 mg/m² IV on days 1 and 2

Obinutuzumab: 1000 mg IV on days 1, 8, and 15

Repeat cycle every 28 days [211].

Bendamustine + Rituximab

Bendamustine: 90 mg/m² IV over 60 minutes on days 1 and 2

Rituximab: 375 mg/m² IV on day 1

Repeat cycle every four weeks for up to six cycles [212, 213].

Lenalidomide + Rituximab

Lenalidomide: 20 mg orally once daily on days 1–21

Rituximab: 375 mg/m² IV on days 1, 8, 15, 22 of cycle 1 and on day 1 of cycles 2–5

Repeat cycle every four weeks until complete response [214, 215].

CVP

Cyclophosphamide: 400 mg/m² orally on days 1–5

Vincristine: 1.4 mg/m² (maximum dose 2 mg) IV on day 1

Prednisone: 100 mg/m² orally on days 1–5

Repeat cycle every three weeks [216].

CHOP

Cyclophosphamide: 750 mg/m² IV on day 1

Doxorubicin: 50 mg/m² IV on day 1

Vincristine: 1.4 mg/m² (maximum dose 2 mg) IV on day 1

Prednisone: 40 mg/m² orally on days 1–5

Repeat cycle every 21 days for eight cycles [220].

R-CHOP

Rituximab: 375 mg/m² IV on day 1

Cyclophosphamide: 750 mg/m² IV on day 1

Doxorubicin: 50 mg/m² IV on day 1

Vincristine: 1.4 mg/m² (maximum dose 2 mg) IV on day 1

Prednisone: 40 mg/m² orally on days 1–5

Repeat cycle every 21 days [217–221].

R-mini-CHOP

Rituximab: 375 mg/m² IV on day 1

Cyclophosphamide: 400 mg/m² IV on day 1

Doxorubicin: 25 mg/m² IV on day 1

Vincristine: 1 mg (maximum dose 2 mg) IV on day 1

Prednisone: 40 mg/m² orally on days 1–5

Repeat cycle every 21 days for six cycles [222].

R-CHOP 14

Rituximab: 375 mg/m² IV on day 1
 Cyclophosphamide: 750 mg/m² IV on day 1
 Doxorubicin: 50 mg/m² IV on day 1
 Vincristine: 1.4 mg/m² (up to a maximum dose of 2 mg) IV on day 1
 Prednisone: 40 mg or 100 mg/m² orally on days 1–5
 Repeat cycle every 14 days for six cycles [223, 224]. Administer granulocyte colony-stimulating factor (G-CSF) on day 4 or 6 of each cycle.

EPOCH

Etoposide: 50 mg/m²/day IV continuous infusion on days 2–4
 Prednisone: 60 mg/m² orally daily on days 1–6
 Vincristine: 0.4 mg/m²/day IV continuous infusion days 2–4
 Doxorubicin: 10 mg/m²/day IV continuous infusion on days 2–4
 Cyclophosphamide: 750 mg/m² IV on day 6
 Repeat cycle every three weeks [225, 226].

EPOCH + Rituximab

Rituximab: 375 mg/m² IV on day 1
 Etoposide: 65 mg/m²/day IV continuous infusion on days 2–4
 Vincristine: 0.5 mg/day IV continuous infusion on days 2–4
 Doxorubicin: 15 mg/m²/day IV continuous infusion on days 2–4
 Cyclophosphamide: 750 mg/m² IV on day 5
 Prednisone: 60 mg/m² orally once daily on days 1–14
 Repeat every three weeks for 4–6 cycles [228].

Ifosfamide + Carboplatin + Etoposide (ICE)

Ifosfamide: 5 g/m² IV admix with mesna 5 g/m² 24-hour continuous IV infusion on day 2
 Carboplatin: AUC of 5, IV bolus
 Etoposide: 100 mg/m² IV bolus days 1–3
 Filgrastim: 5 µg/kg/day SC on days 7–14 for cycles 1 and 2, then 10 µg/kg/day for all subsequent cycles
 Repeat cycle every two weeks [229].

Rituximab + Ifosfamide + Carboplatin + Etoposide (RICE)

Rituximab: 375 mg/m² IV on day 1
 Ifosfamide: 5 g/m² admix with mesna 5 g/m² IV continuous 24 hours' infusion on day 4
 Carboplatin: AUC of IV bolus on day 4
 Etoposide: 100 mg/m² IV bolus daily on days 3–5
 Filgrastim: 5 µg/kg/day on days 7–14 for cycles 1 and 2, then 10 µg/kg/day SC for all subsequent cycles
 Repeat cycle every two weeks [230, 231].

Fludarabine + Cyclophosphamide

Fludarabine: 25 mg/m² IV daily on days 1–3
 Cyclophosphamide: 300 mg/m² IV daily on days 1–3
 Repeat cycle every 28 days for a total of six cycles [343].

Fludarabine + Cyclophosphamide + Rituximab (FCR)

Fludarabine: 25 mg/m² IV on days 1–3
 Cyclophosphamide: 1 g/m² IV on day 1
 Rituximab: 375 mg/m² IV on day 4
 Repeat cycle every four weeks for four cycles [232].

DHAP (Salvage Therapy)

Cisplatin: 100 mg/m² IV 24 hours' continuous infusion on day 1
 Cytarabine: 2 g/m² IV over three hours every 12 hours for two doses on day 2 after completion of cisplatin infusion
 Dexamethasone: 40 mg orally or IV on days 1–4
 Repeat cycle every 3–4 weeks for 6–10 cycles [233].

DHAP + Rituximab (Salvage Therapy)

Cisplatin: 100 mg/m² IV 24 hours' continuous infusion on day 1
 Cytarabine: 2 g/m² IV over three hours every 12 hours for two doses on day 2 after completion of cisplatin infusion
 Dexamethasone: 40 mg orally or IV on days 1–4
 Rituximab: 375 mg/m² IV to prior to DHAP
 Repeat cycle every 3–4 weeks for 6–10 cycles [234, 235].

ESHAP (Salvage Therapy)

Etoposide: 40 mg/m² IV daily on days 1–4
 Methylprednisolone: 500 mg IV daily on days 1–5
 Cisplatin: 25 mg/m² IV daily continuous infusion on days 1–4
 Cytarabine: 2 g/m² IV over 2–3 hours on day 5 after completion of cisplatin and etoposide
 Repeat cycle every 21 days [236].

ESHAP + Rituximab (Salvage Therapy)

Etoposide: 40–60 mg/m² IV infusion over one hour daily on days 1–4
 Methylprednisolone: 250–500 mg IV infusion over 15 minutes daily on days 1–5
 Cisplatin: 25 mg/m² IV continuous infusion daily on days 1–4
 Cytarabine: 2 g/m² IV infusion over two hours on day 5 after completion of cisplatin and etoposide
 Rituximab: 375 mg/m² IV on day 1 or 5
 Repeat cycle every 21 days for 3–4 cycles [237].

MINE

Mesna: 2 g/m² IV on days 1–3
 Ifosfamide: 2 g/m² IV on days 1–3
 Mitoxantrone: 8 mg/m² IV on day 1
 Etoposide: 100 mg/m² IV on days 1–3
 Repeat cycle every 28 days for two cycles [238, 239, 344]

MINE + Rituximab

Mesna: 2.6 g/m² IV on days 1–3
 Ifosfamide: 2.6 g/m² IV on days 1–3
 Mitoxantrone: 8 mg/m² IV on day 1
 Etoposide: 300 mg/m² IV on days 1–3
 Rituximab: 400 mg/m² IV on day 1
 Repeat cycle every 28 days for two cycles [238, 239, 344].

Mini-BEAM

Busulfan: 60 mg/m² on day 1
 Etoposide: 75 mg/m² IV on days 2–5
 Cytarabine: 100 mg/m² every 12 hours on days 2–5
 Melphalan: 30 mg/m² on day 6
 Repeat cycle every 28 days [345, 346].

Gemcitabine + Vinorelbine (GV)

Gemcitabine: 1000 mg/m² IV over 30 minutes on days 1 and 8
 Vinorelbine: 30 mg/m² IV on days 1 and 8
 Repeat cycle every 21 days for six cycles [347].

Gemcitabine + Dexamethasone + Cisplatin (GDP)

Gemcitabine: 1000 mg/m² IV over 30 minutes on days 1 and 8
 Dexamethasone: 40 mg orally in divided doses daily on days 1–4
 Cisplatin: 75 mg/m² IV over 60 minutes on day 1
 Repeat cycle every 21 days [348].

Gemcitabine + Methylprednisolone + Cisplatin (GEM-P)

Gemcitabine: 1000 mg/m² IV over 30 minutes on days 1, 8, and 15
 Cisplatin: 100 mg/m² IV over four hours on day 15, four hours after gemcitabine infusion
 Methylprednisolone: 1000 mg/day IV over 15 minutes on days 1–5

Rituximab + Gemcitabine + Oxaliplatin (R+GEMOX)

Rituximab: 375 mg/m² IV on day 1
 Gemcitabine: 1000 mg/m² IV over 30 minutes on day 1
 Oxaliplatin: 100 mg/m² IV over on day 1
 Repeat cycle every 14 days for 6–8 cycles [350].

Ifosfamide + Etoposide + Cytarabine + Dexamethasone (IVAD)

Ifosfamide: 1500 mg/m² admix with mesna 1500 mg/m² IV on days 1–5
 Etoposide: 100 mg/m² IV on days 1–5
 Cytarabine: 100 mg/m² IV on days 1–5
 Dexamethasone: 40 mg on days 1–5
 Repeat cycle every 21 days [351].

Polatuzumab Vedotin + Rituximab + Bendamustine

Polatuzumab vedotin: 1.8 mg/kg IV on day 1
 Rituximab: 375 mg/m² IV on day 1
 Bendamustine: 90 mg/m²/day IV on days 1 and 2
 Repeat cycle every 21 days for six cycles [352].

4.11 Cutaneous T-Cell Lymphoma Treatment Regimens**Belinostat**

1000 mg/m² IV on days 1–3
 Repeat cycle every three weeks [240].

Gemcitabine

1200 mg/m² IV over 30 minutes on days 1, 8, and 15
 Repeat cycle every 28 days for three cycles [342].

Romidespin

14 mg/m² IV on days 1, 8, and 15
 Repeat cycle every 28 days and continue until disease progression or unacceptable toxicity occurs [355].

Mogamulizumab-kpkc

mg/kg IV on days 1, 8, 15, and 22 of the first 28 days cycle then on days 1 and 8 of each subsequent cycle. Continue until disease progression or intolerable toxicity [356].

Vorinostat

400 mg orally once daily
 Continue until disease progression or unacceptable toxicity [357, 358].

Bortezomib

1.3 mg/m² intravenously on days 1, 4, 8, and 11, followed by a 1-week rest period (one cycle)
 Repeat cycle every 21 days for a total of six cycles [359].

Alemtuzumab

30 mg three times a week for up to 12 weeks [361].

Brentuximab Vedotin

1.8 mg/kg every 21 days for a maximum of eight doses [360].

Pegylated Liposomal Doxorubicin

20–40 mg/m² IV every two weeks [362].

Bexarotene

300 mg/m² orally once daily

Continue until disease progression or unacceptable toxicity occurs [363].

4.12 Primary CNS Lymphoma Treatment Regimens

High-Dose Methotrexate

1–8 g/m² IV on day 1

Repeat cycle every 14 days [241].

High-Dose Cytarabine

3 g/m² IV over three hours, every 12 hours for four doses on days 1 and 2

Repeat cycle every 28 days or until disease progression or intolerable toxicity [242].

Topotecan

1.5 mg/m² IV on days 1–5

Repeat cycle every 21 days [243].

Temozolomide

150 mg/m²/day orally on days 1–5

Repeat cycle every 28 days [244].

Ibrutinib

560 mg or 840 mg orally once daily

Continue until disease progression or unacceptable toxicity occurs [364].

Nivolumab

3 mg/kg IV every two weeks

Repeat cycle every two weeks [366].

Rituximab

375 mg/m² as a single IV infusion every week for up to eight weeks [365].

Thiotepa

50–65 mg/m² IV over eight hours' infusion daily

Continue until disease progression or unacceptable toxicity [369].

Lenalidomide

10–30 mg orally daily on days 1–21

Repeat cycle every 28 days (3 weeks on/1 week off) [368].

Lenalidomide + Rituximab

Rituximab: 375 mg/m² IV on day 1

Lenalidomide: 20 mg orally once daily on days 1–21

Repeat cycle every 28 days [367].

4.13 Multiple Myeloma Treatment Regimen

Single-Agent Regimens

Bendamustine

80–150 mg/m² in 500 ml NaCl 0.9%, IV infusion over 30 minutes on days 1 and 2

Repeat cycle every four weeks until maximal response, disease progression, or intolerable toxicity [245, 246].

Belantamab Mafodotin-blmf

2.5 mg/kg or 3.4 mg/kg IV on day 1

Repeat cycle every 21 days and continue until disease progression or unacceptable toxicity [247].

Bortezomib

1.3 mg/m² IV or SC on days 1, 4, 8, and 11

Repeat cycle every three weeks for two years or until disease progression or unacceptable toxicity [248].

Carfilzomib

20 mg/m² IV infusion 2–10 minutes on days 1, 2, 8, 15, and 16. After cycle 1, increase the dose to 27 mg/m² IV infusion

Repeat cycle every 28 days for 12 cycles [250].

Daratumumab

16 mg/kg IV infusion once weekly (weeks 1–8); reduce the frequency to once every two weeks (weeks 9–24); followed by once every four weeks (week 25 and thereafter)

Continue until disease progression [251].

Lenalidomide

10 mg orally once daily on days 1–21

Repeat cycle every 28 days until disease progression or the development of unacceptable toxic effects [254, 255].

Ixazomib

3 mg orally once on days 1, 8, and 15

Repeat cycle every 28 days [256].

Melphalan

140 mg/m² IV on day 1

Repeat cycle every 28–42 days [257].

Pomalidomide

4 mg orally daily on days 1–21
Repeat cycle every 28 days [258].

Combination Regimens

Combination-regimens for Multiple Myeloma

Bortezomib + Dexamethasone

Bortezomib: 1.3 mg/m² IV or SC on days 1, 4, 8, and 11
Dexamethasone: 40 mg orally on days 1 to 4 (all cycles) and days 9 to 12
(cycles 1 and 2)
Repeat cycle every three weeks [259, 260].

Bortezomib + Liposomal Doxorubicin

Bortezomib: 1.3 mg/m² IV bolus or SC on days 1, 4, 8, and 11
Liposomal doxorubicin: 30 mg/m² IV infusion over 60 minutes on day 4 of each
cycle
Repeat cycle every three weeks until disease progression, or the development of
unacceptable toxic effects [261].

Lenalidomide + Dexamethasone

Lenalidomide: 25 mg orally once daily on days 1–21
Dexamethasone: 40 mg orally on days 1, 8, 15 and 22
Repeat cycle every four weeks until maximal response, disease progression, or
unacceptable toxicity [262–264].

Carfilzomib + Dexamethasone

Carfilzomib: 20 mg/m² IV over 30 minutes on days 1, 8, and 15 of cycle 1,
and then
70 mg/m² IV on days 1, 8, and 15 for all subsequent cycles
Dexamethasone: 40 mg orally on days 1, 8, and 15 for all cycles and 22 (cycles
1–9 only)
Repeat cycle every 28 days until disease progression or unacceptable toxicity [265].

Pomalidomide + Dexamethasone

Pomalidomide: 4 mg orally once daily on days 1–21
Dexamethasone: 40 mg orally once on days 1, 8, and 15
Repeat cycle every 28 days and continue until disease progression, or intolerable
toxicity [266–270].

Ixazomib + Dexamethasone

Ixazomib: 5.5 mg orally on days 1, 8, and 15
Dexamethasone: 20 mg orally on days 1, 2, 8, 9, 15 and 16
Repeat cycle every 28 days and continue until disease progression or intolerable
toxicity [271, 272].

Thalidomide + Dexamethasone

Thalidomide: 200 mg orally once daily on days 1–28
 Dexamethasone: 40 mg orally on days 1–4, 9–12, and 17–20 (odd cycles), and
 40 mg orally once on days 1–4 (even cycles)
 Repeat cycle every 28 days [273].

Selinexor + Dexamethasone

Selinexor: 80 mg orally on days 1 and 3 (or twice weekly)
 Dexamethasone: 20 mg orally on days 1 and 3 (or twice weekly)
 Repeat cycle weekly and continue until disease progression or unacceptable
 toxicity [274, 275].

Panobinostat + Carfilzomib

Panobinostat: 30 mg orally on days 1, 3, 5, 15, 17, and 19
 Carfilzomib: 56 mg/m² IV over 30 minutes on days 1, 2, 8, 9, 15, and 16
 Repeat cycle every 28 days until disease progression, or intolerable toxicity
 [276, 277].

Lenalidomide + Bortezomib + Dexamethasone (RVD)

Lenalidomide: 5–25 mg orally once daily on days 1–14
 Bortezomib: 1–1.3 mg/m² IV or SC on days 1, 4, 8, and 11
 Dexamethasone: 20 mg or 40 mg orally once daily on days 1, 2, 4, 5, 8, 9, 11,
 and 12
 Repeat cycle every 21 days for a total of eight cycles [278].

Bortezomib + Cyclophosphamide + Dexamethasone (BCD)

Bortezomib: 1.3 mg/m² IV or SC on days 1, 4, 8, and 11
 Cyclophosphamide: 300 mg/m² orally once daily on days 1, 8, 15, and 22
 Dexamethasone: 40 mg orally once daily on days 1–4, 9–12, and 17–20
 Repeat cycle every four weeks for 3–4 cycles [279–282].

Bortezomib + Doxorubicin + Dexamethasone

Bortezomib: 1.3 mg/m² IV or SC on days 1, 4, 8, and 11
 Doxorubicin: 9 mg/m² IV continuous infusion over 24 hours daily on days
 1–4
 Dexamethasone: 40 mg orally once daily on days 1–4, 9–12, and 17–20
 Repeat cycle every 21 days for 3–4 cycles [283].

Ixazomib + Lenalidomide + Dexamethasone

Ixazomib: 4 mg orally once daily on days 1, 8, and 15
 Lenalidomide: 25 mg orally once daily on days 1–21
 Dexamethasone: 40 mg orally once daily on days 1, 8, 15, and 22
 Repeat cycle every 28 days until disease progression, or intolerable toxicity [284].

Carfilzomib + Lenalidomide + Dexamethasone (CRD)

Carfilzomib: 20 or 27 or 36 mg/m² IV on days 1, 2, 8, 9, 15, and 16 and 1, 2, 15, and 16 after cycle 8
 Lenalidomide: 25 mg orally once daily on days 1–21
 Dexamethasone: 40 mg orally once daily on days 1, 8, 15, and 22
 Repeat cycle every 28 days and continue until disease progression [285, 286].

Bortezomib + Thalidomide + Dexamethasone

Bortezomib: 1.3 mg/m² IV or SC on days 1, 4, 8, and 11
 Thalidomide: 50–200 mg (escalating doses) orally once daily on days 1–21
 Dexamethasone: 40 mg orally once daily on days 1–4 and 9–12
 Repeat cycle every 21 days for 3–4 cycles [287–290].

Isatuximab + Pomalidomide + Dexamethasone

Isatuximab: 10 mg/kg IV weekly for cycle 1, then every two weeks from cycle 2 and thereafter
 Pomalidomide: 4 mg orally once daily on days 1–21
 Dexamethasone: 40 mg orally once daily on days 1, 8, 15, and 22
 Repeat cycle every 28 days [370].

Daratumumab + Bortezomib + Dexamethasone

Daratumumab: 16 mg/kg IV weekly during cycles 1–3, 16 mg/kg IV on day 1 of cycles 4–9 and thereafter
 Bortezomib: 3 mg/m² IV or SC on days 1, 4, 8, and 11 on cycles 1–8
 Dexamethasone: 40 mg orally once daily on days 1, 2, 4, 5, 8, 9, 11, and 12 on cycles 1–8 and thereafter
 Repeat cycle every 28 days and continue until disease progression, or intolerable toxicity [291].

Daratumumab + Lenalidomide + Dexamethasone

Daratumumab: 16 mg/kg IV weekly on cycles 1 and 2, 16 mg/kg IV every two weeks on cycles 3–6, and every four weeks thereafter
 Lenalidomide: 25 mg orally once daily on days 1–21
 Dexamethasone: 40 mg orally on days 1, 8, 15, and 22
 Repeat cycle every 28 days and continue until maximal response, disease progression, or intolerable toxicity [292].

Elotuzumab + Lenalidomide + Dexamethasone

Elotuzumab: 10 mg/kg IV on days 1, 8, and 22 for cycles 1 and 2, followed by 10 mg/kg IV on days 1 and 15 for all subsequent cycles
 Lenalidomide: 25 mg orally once daily on days 1–21 for all cycles
 Dexamethasone: 40 mg during the week without elotuzumab and intravenously at a dose of 8 mg plus 28 mg orally on the day of elotuzumab administration.
 Repeat cycle every 28 days until disease progression, or unacceptable toxicity [293, 294].

Bendamustine + Bortezomib + Dexamethasone

Bendamustine: 70 mg/m² IV on days 1 and 8
 Bortezomib: 1.3 mg/m² IV or SC on days 1, 4, 8, and 11
 Dexamethasone: 20 mg orally 1–2, 4–5, 8–9, and 11–12 before bendamustine and bortezomib for the first two cycles, then 20 mg IV or PO on days 1, 8, 15, and 22 for all subsequent cycles after bendamustine and bortezomib

Repeat cycle every 28 days [295].

Bendamustine + Lenalidomide + Dexamethasone

Bendamustine: 75 mg/m² IV over 30 minutes on days 1 and 4
 Lenalidomide: 10 mg orally once daily on days 1–21
 Dexamethasone: 20 mg orally on days 1, 8, 15, and 22
 Repeat cycle every 28 days for four cycles and continue until disease progression, or unacceptable toxicity [296].

Elotuzumab + Bortezomib + Dexamethasone

Elotuzumab: 10 mg/kg IV on days weekly for cycles 1 and 2, on days 1 and 11 for cycles 3–8, and then on days 1 and 15 thereafter
 Bortezomib: 1.3 mg/m² IV or SC on days 1, 4, 8, and 11 during cycles 1–8 and then on days 1, 8, and 15 thereafter
 Dexamethasone: 20 mg orally on non-elotuzumab dosing days, and as 8 mg orally plus 8 mg IV on elotuzumab dosing days.

Repeat cycle every 21 days for cycles 1–8, and then in 28 days' cycle until disease progression, or intolerable toxicity [297].

Pomalidomide + Bortezomib + Dexamethasone

Pomalidomide: 4 mg orally once daily on days 1–21
 Bortezomib: 1.3 mg/m² IV or SC on days 1, 8, 15, and 22
 Dexamethasone: 40 mg orally once on days 1, 8, 15, and 22
 Repeat cycle every 28 days [298–300].

Pomalidomide + Carfilzomib + Dexamethasone

Pomalidomide: 4 mg orally once daily on days 1–21
 Carfilzomib: 20 mg/m² or 27 mg/m² IV on days 1, 2, 8, 9, 15, and 16
 Dexamethasone: 40 mg orally or IV on days 1, 8, 15, and 22
 Repeat cycle every 28 days [301, 302].

Cyclophosphamide + Lenalidomide + Dexamethasone

Cyclophosphamide: 500 mg orally once daily on days 1, 8, 15, and 22
 Lenalidomide: 10 mg orally once daily on days 1–21
 Dexamethasone: 40 mg orally once daily on days 1–4 and 12–15
 Repeat cycle every 28 days for a maximum of nine cycles [303].

Panobinostat + Bortezomib + Dexamethasone

Panobinostat: 20 mg orally once daily on days 1, 3, 5, 8, 10, and 12
 Bortezomib: 1.3 mg/m² IV or SC on days 1, 4, 8, and 11
 Dexamethasone: 20 mg orally once daily on days 1, 2, 4, 5, 8, 9, 11, and 12
 Repeat cycle every 21 days [304, 305].

Pomalidomide + Cyclophosphamide + Dexamethasone

Pomalidomide: 4 mg orally once daily on days 1–21
 Cyclophosphamide: 300–500 mg (dose escalation) orally once daily on days 1, 8, and 15
 Dexamethasone: 40 mg orally once daily on days 1, 8, 15, and 22
 Repeat cycle every 28 days [306].

Melphalan + Prednisone + Thalidomide (MPT)

Melphalan: 0.25 mg/kg orally once on days 1–4
 Prednisone: 1.5 mg/kg orally on days 1–4
 Thalidomide: 50–100 mg orally once daily on days 1–28
 Repeat cycle every four weeks [307].

Melphalan + Prednisone + Lenalidomide (MPL)

Melphalan: 0.18–0.25 mg/kg orally once on days 1–4
 Prednisone: 2 mg/kg orally on days 1–4
 Lenalidomide: 5–10 mg orally once daily on days 1–21
 Repeat cycle every four weeks [308].

Vincristine + Doxorubicin + Dexamethasone (VAD)

Vincristine: 0.4 mg/day IV continuous infusion on days 1–4
 Doxorubicin: 9 mg/m²/day IV continuous infusion on days 1–4
 Dexamethasone: 40 mg orally once daily on days 1–4 (all cycles) and days 9–12, and days 17–20 (cycles 1 and 2)
 Repeat cycle every 28 days [309].

Bortezomib + Melphalan + Prednisone

Bortezomib: 1–1.3 mg/m² IV or SC on days 1, 4, 8, 11, 22, 25, 29, and 32 during cycles 1 to 4 and on days 1, 8, 22, and 29 during cycles 5 to 9.
 Melphalan: 9 mg/m² orally once on days 1–4
 Prednisone: 60 mg/m² orally on days 1–4
 Repeat cycle every six weeks for nine cycles [310].

Daratumumab + Bortezomib + Thalidomide + Dexamethasone

Daratumumab: 16 mg/kg IV once weekly in cycles 1 and 2 and once every two weeks during induction cycles 3 and 4
 Bortezomib: 1.3 mg/m² IV or SC on days 1, 4, 8, and 11
 Thalidomide: 100 mg orally daily
 Dexamethasone: 40 mg orally once on days 1, 2, 8, 9, 15, 16, 22, and 23 of cycles 1 and 2; 40 mg on days 1 and 2 of cycles 3 and 4
 Repeat cycle every 28 days for four cycles [312].

Dexamethasone + Thalidomide + Cisplatin + Doxorubicin + Cyclophosphamide + Etoposide + Bortezomib (VTD-PACE)

Bortezomib: 1 mg/m² IV or SC on days 1, 4, 8, and 11
 Thalidomide: 200 mg orally daily on days 1–4, then 50 mg daily
 Dexamethasone: 40 mg orally once on days 1–4
 Cisplatin: 10 mg/m²/day IV continuous infusion over 24 hours on days 1–4
 Doxorubicin: 10 mg/m²/day IV continuous infusion over 24 hours on days 1–4
 Cyclophosphamide: 400 mg/m²/day IV continuous infusion over 24 hours on days 1–4
 Etoposide: 40 mg/m²/day IV continuous infusion over 24 hours on days 1–4
 Continue until disease progression [313].

Dexamethasone + Cyclophosphamide + Etoposide + Cisplatin (DCEP)

Dexamethasone: 40 mg orally once on days 1–4
 Cyclophosphamide: 400 mg/m²/d IV continuous infusion over 24 hours on days 1–4
 Etoposide: 40 mg/m²/d IV continuous infusion over 24 hours on days 1–4
 Cisplatin: 15 mg/m²/d IV continuous infusion over 24 hours on days 1–4
 Continue until disease progression [313].

Dexamethasone + Cyclophosphamide + Vincristine + Doxorubicin (CVAD)

Dexamethasone: 40 mg orally on days 1–5 and 11–14
 Cyclophosphamide: 300 mg/m² IV over three hours every 12 hours on days 1–3
 Vincristine: 2 mg IV continuous infusion over 48 hours on day 4 and 2 mg IV over 10 min on day 11
 Doxorubicin: 50 mg/m² IV continuous infusion over 48 hours on day 4
 Continue until disease progression [313].

4.14 Risk Factors and Possible Preventions

The causes of many blood cancers are still unknown. Reducing risk factors such as avoiding exposure to radiation, chemicals such as pesticides or benzene, and smoking or tobacco in any form can help. Maintaining a healthy lifestyle and healthy diet may reduce the risk of developing a variety of blood cancers.

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5

Brain and Spinal Cord Tumors

5.1 Introduction

There are several types of cancers that affect the brain and spinal cord, named on the basis of the type of cell in which they appear and the initial location of the tumor in the central nervous system (CNS) [1–8].

Cancers of the CNS are further classified according to grade, which defines its severity. Grades for brain and spinal cord cancers are I, II, III, or IV. A Grade I tumor is benign, whereas Grades II, III, and IV are increasingly serious in terms of their rate of growth and extent of invasion to surrounding tissues (Figure 5.1).

Tumors that originate in the brain are called primary brain tumors, and they may be benign (not cancerous) or malignant (cancerous) [9–28]. For example, an astrocytic tumor starts in star-shaped cells in the brain called *astrocytes*, which normally function to keep nerve cells healthy. Glioblastoma multiforme (GBM) is an astrocytic tumor considered to be the most aggressive of all [29–31].

5.2 Genes Associated with Brain Cancer

Mutations and deletions of tumor suppressor genes including in the cell checkpoint genes *TP53* and *CHEK2 P53* may cause some forms of brain tumor. Other gene mutations for neurofibromatosis and tuberous sclerosis include *NF1*, *NF2*, *TSC1*, and *TSC2*. These are controlled by the downregulation of growth-promoting signal transduction pathways in the cell.

5.3 Types of Primary Brain Tumors for Adults

Of the many types of primary brain tumors in adults, the most common are **astrocytoma**, **oligodendroglioma**, and **meningioma**. Primary brain tumors are named according to the type of cells or part of the brain where they start, with most beginning in glial cells (Figure 5.2). Glial cells are not nerve cells, but line the

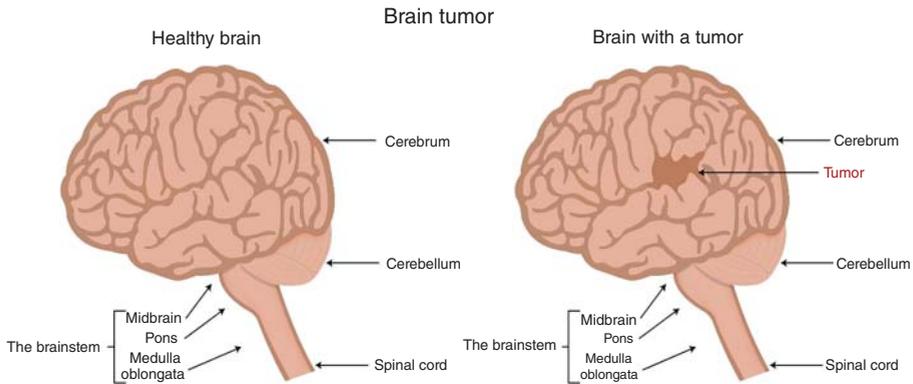


Figure 5.1 Healthy brain versus cancer-affected.

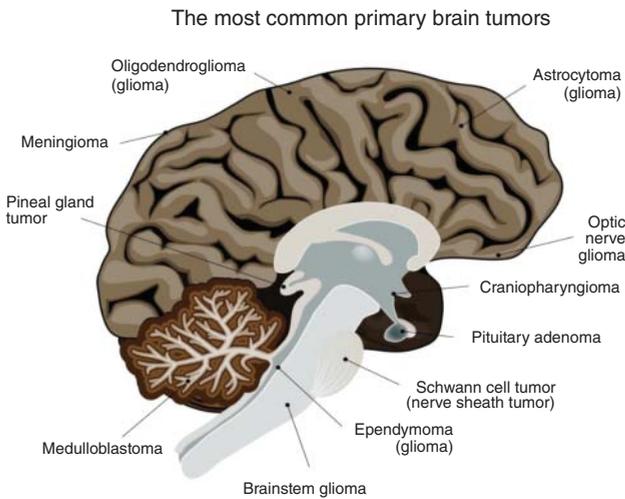


Figure 5.2 Brain cancers are named according to the location in the brain where they originate.

outside of the neurons to lend protection and support. A tumor originating in a glial cell is called a *glioma*. There are many types of gliomas, categorized by the location of the tumor. Common types of gliomas are:

5.3.1 Astrocytoma

The tumor arises in the above-mentioned astrocytes, which are a type of glial cell [9, 10]. An astrocytoma can be of any grade. In adults, this type of tumor most frequently arises in the cerebrum.

- Grade I or II astrocytoma, referred to as a low-grade glioma.

- Grade III astrocytoma, sometimes called a high-grade or anaplastic astrocytoma.
- Grade IV astrocytoma, otherwise called GBM or malignant astrocytic glioma.

5.3.2 Oligodendroglioma

The tumor develops in glial cells called *oligodendrocytes*, which make the fatty substance called myelin that covers and protects neurons. This type of glioma usually occurs in the cerebrum, and it most commonly affects middle-aged adults [11–14]. An oligodendroglioma can be of Grade II or III.

5.3.3 Meningioma

Meningiomas are usually slow-growing, benign tumors which arise in the outer coverings of the brain called the *meninges*, located just beneath the skull. This type of tumor accounts for about one-third of all adult brain tumors [15–18]. Although generally encountered as Grade I tumors, meningiomas can also be the more serious Grade II or III types.

5.4 Types of Brain Cancer for Children

Among children, the most common primary tumor types are:

5.4.1 Medulloblastoma

The tumor usually forms in the cerebellum. Sometimes referred to as a primitive neuroectodermal tumor, this is a Grade IV brain cancer [19–23].

5.4.2 Grade I or II Astrocytoma

In children, this Grade I tumor can develop anywhere in the brain. The most common astrocytoma among children is juvenile pilocytic astrocytoma.

5.4.3 Ependymoma

This type of tumor originates in cells that line the ventricles or central canal of the spinal cord. It can be Grade I, II, or III, and is seen most commonly in children and young adults [24–26].

5.4.4 Brainstem Glioma

This tumor develops in the brainstem and can be low- or high-grade. The most common category of brainstem glioma in children is called diffuse intrinsic pontine

glioma, which is difficult to treat because it spreads diffusely throughout normal brain stem cells and is not localized in a cohesive tumor [27, 28].

5.5 Brain Tumor Symptoms

The symptoms of a brain tumor vary mostly depending on its size, location, and rate of growth. General signs and symptoms may include:

- New onset of headaches or changes in a prior experience of headaches
- More frequent and severe headaches
- Nausea or vomiting without any prior reason
- Blurred vision, double vision, or loss of peripheral vision
- Slowly loss of sensation or movement in an arm or a leg
- Difficulty with balance
- Difficulty in speech
- Forgetting about everyday matters
- Personality or behavioral changes
- Seizures, without previous history of seizures
- Problems in hearing

5.6 Diagnosis

If a brain tumor is suspected [32, 33], physicians may recommend a number of tests and procedures as follows:

5.6.1 Neurological Exam

A neurological exam may include, among other things, checking a patient's vision, hearing, balance, coordination, strengths, and reflexes. Difficulty in one or more of these areas provides clues about the part of the brain possibly affected.

5.6.2 Imaging Tests

Various types of imaging procedures assist specialists in detecting, diagnosing, and establishing the extent of brain cancer as well as other forms of cancer. **Magnetic resonance imaging (MRI)** is a screening test that combines powerful magnets and radio waves to create detailed images of soft tissues within the body. An MRI may also involve the injection of a contrast agent to create clearer, more informative pictures.

Other imaging tests include **computed tomography (CT)**, a procedure utilizing X-rays and a computer, which together generate a series of very detailed pictures of the brain. Sometimes CT scans include prior administration of a dye, to give images increased contrast. **Positron emission tomography (PET)** involves the use of a dye containing a radioactive tracer, which shows up in higher concentrations in parts

of the body where there is a high level of chemical activity, one indication of the presence of disease. PET scans may be for brain imaging, but this scan is generally not as useful for capturing images of brain cancer as it is for other types of cancer.

5.6.3 Biopsy

Collecting and testing a sample of abnormal tissue helps in diagnosing the nature and extent of a disease, in this case, cancer in the brain or spinal cord. Tissue for biopsy can be obtained through needle extraction, or in the course of surgery to remove the brain tumor. The sample is viewed under a microscope to determine if it is cancerous or benign. Further, high-level laboratory tests can also provide information about a patient's prognosis and treatment options.

5.7 Methods of Treatment

Treatment for a brain tumor depends on the type, size, and location of the tumor, as well as the patient's overall health and preferences [34–107].

5.7.1 Surgery

If the brain tumor is located in a place accessible via surgery, physicians will operate to remove as much of it as possible.

5.7.2 Radiation Therapy

Tumor cells are destroyed through irradiation with high-energy beams, such as X-rays or protons. Radiation therapy is applied with various types of equipment determined by the physician, in a process called External Beam Radiation. In rare cases, radiation is administered through brachytherapy in which radioactive material is placed inside a patient's body, close to or within the tumor.

5.7.3 Radiosurgery

As the name implies, radiation is used during surgery to target and destroy cancerous areas. In stereotactic radiosurgery, a highly focused beam of radiation is targeted to destroy tumor cells in a small area in order to minimize harm to surrounding healthy tissue and structures. In the case of brain tumors, radiosurgery is conducted with Gamma Knife or Linear Accelerator (LINAC) technology.

5.7.4 Chemotherapy

For the treatment of some types of brain tumors, the oral chemotherapy drug temozolomide (Temodar) is currently the gold standard. Other chemotherapy agents used with or without temozolomide are carboplatin, carmustine, cisplatin,

cyclophosphamide, etoposide, irinotecan, lomustine, methotrexate, procarbazine, and vincristine. The chemotherapy drug utilized is dependent on the type of cancer. Common side effects of chemotherapy are nausea, vomiting, and hair loss.

5.7.5 Targeted Drug Therapy

This type of treatment blocks the abnormal activity of certain molecules found in cancer cells, which are required for the progression and growth of these cells. Some targeted therapy drugs kill cancer cells, whereas others inhibit their proliferation. Currently, bevacizumab (Avastin, Mvasi, Zirabev), everolimus (Afinitor), and naxitamab-ggqk (Danyelza) are targeted therapy drugs available for treating certain types of brain tumors, and many more are pending further investigation through clinical trials. Positive clinical trial results promise a greater selection of these drugs for treatment in the near future.

5.8 Treatment Regimens

Neoadjuvant/adjuvant/advanced disease

Single-Agent Regimens

Bevacizumab

10 mg/kg IV over 30 minutes on day 1
Repeat cycle every two weeks [55, 69, 78–82].

Carboplatin

560 mg/m² IV at 4-week intervals
Continued until disease progression or intolerable toxicity, or for 12 additional courses [83].

Carmustine

150–200 mg/m² IV on day 1
Repeat cycle every 6–8 weeks [84].

Cyclophosphamide

750 mg/m² IV on days 1 and 2
Repeat cycle every 28 days [85, 86].

Etoposide

50 mg/day IV
Continue until the neutrophil count dropped to $<1.0 \times 10^9/l$ or the platelets fell to $<75 \times 10^9/l$ [63, 87].

Irinotecan

350 mg/m² IV infusion over 90 minutes on day 1
Repeat cycle every 21 days [88].

or

125 mg/m² IV infusion over 90 minutes weekly
Repeat cycle every six weeks [89].

Lomustine

100–130 mg/m² orally once on day 1
Repeat cycle every six weeks [90, 91].

Procarbazine

150 mg/m² orally once daily on days 1–28
Repeat cycle every eight weeks [92].

Temozolomide

150 mg/m² orally once daily on days 1–5
Repeat cycle every 28 days. Increase the temozolomide dose to 200 mg/m² per day if tolerated.

or

75 mg/m² orally once daily on days 1–49
Repeat cycle every 11 weeks (7 weeks on/4 weeks off), a total of six cycles or continue until disease progression or unacceptable toxicity [51, 64, 66, 67, 93–95].
For children/adolescents: 200 mg/m² by mouth on days 1–5 per month.

Temozolomide + Radiation Therapy (for Adjuvant Therapy)**Combination Regimens**

Temozolomide: 75 mg/m² orally once daily for six weeks
Radiation: 2 Gy/day for five days per week, total six weeks
Repeat temozolomide every 28 days for up to six cycles [96].

Temozolomide + Bevacizumab

Temozolomide: 150–200 mg/m² orally once daily on days 1–5
Bevacizumab: 10 mg/kg IV on days 1 and 14
Repeat cycle every 14 days [97].

Temozolomide + Lomustine

Temozolomide: 100 mg/m² orally once daily on days 2–6
Lomustine: 100 mg/m² orally once on day 1
Repeat cycle every 28 days for up to six cycles [98].

Irinotecan + BevacizumabIrinotecan: 125 mg/m² IV on day 1

Bevacizumab: 10 mg/kg IV on day 1

Repeat cycle every two weeks for up to six cycles [55, 69, 99, 100].

Cisplatin + EtoposideCisplatin: 25–30 mg/m²/day IV on days 1–3Etoposide: 100–150 mg/m²/day IV on days 1–3

Repeat cycle every four weeks [101].

Bevacizumab + Carboplatin

Bevacizumab: 10 mg/kg IV on day 1

Carboplatin: AUC of 4–6 mg/ml/min

Repeat two doses of carboplatin (every 28 days) and three doses of bevacizumab (every 14 days) for up to six weeks [102, 103].

Carboplatin + Teniposide (for Glioblastoma)Carboplatin: 350 mg/m² IV on day 1Teniposide: 50 mg/m² IV on days 1–3

Repeat cycle every 28 days [104].

Carboplatin + Irinotecan + Bevacizumab

Carboplatin AUC of 4, IV on day 1

Irinotecan 340 mg/m² IV on days 1 and 14

Bevacizumab 10 mg/kg IV on days 1 and 14

Repeat cycle every four weeks [105].

PCVProcarbazine: 60 mg/m² orally once daily on days 8–21Lomustine (CCNU): 110 mg/m² orally on day 1Vincristine: 1.4 mg/m² IV on days 8 and 29

Repeat cycle every eight weeks for a total of six cycles [50, 106, 107].

Vincristine + Cisplatin + Lomustine (for Adult Medulloblastoma)Vincristine: 1.5 mg/m² IV on days 2, 8, and 15Cisplatin: 75 mg/m² IV on day 2Lomustine: 75 mg/m² orally on day 1

Patients should be closely monitored for neurologic toxicity with periodic exams [82].

Vincristine + Cisplatin + CyclophosphamideVincristine: 1.5 mg/m² IV on days 2, 8, and 15Cisplatin: 75 mg/m² IV on day 1Cyclophosphamide: 1000 mg/m² IV on days 22, 23

Patients should be closely monitored for neurologic toxicity with periodic exams [82].

Systemic Therapy for Intracranial and Spinal Ependymoma

Carboplatin

560 mg/m² IV at 4-week intervals

Continued until disease progression, unacceptable toxicity [83].

Carboplatin + Teniposide

Carboplatin: 350 mg/m² IV on day 1

Teniposide: 50 mg/m² IV on days 1–2

Repeat cycle every four weeks [51, 66].

Cisplatin + Etoposide

Cisplatin: 25 mg/m² IV on days 1–3

Etoposide: 100 mg/m² IV on days 1–3

Repeat cycle every four weeks [101].

Temozolomide

75 mg/m² orally once daily on days 1–49

Repeat cycle every 11 weeks (7 weeks on/4 weeks off) for six cycles [51].

5.9 Post-Treatment Rehabilitation

Brain tumors develop in parts of the brain that control motor skills, speech, vision, and cognition (thinking). As such, rehabilitation may be a necessary part of recovery after treatment. Depending on a patient's needs, the physician may recommend:

- Physical therapy to help patients regain lost motor skills or muscular strength.
- Occupational therapy to support patients in returning to normal daily activity, including employment.
- Speech therapy with specialists in speech difficulties (speech pathologists) to assist patients having post-treatment speech impairment.
- Tutoring for school-aged children whose memory and cognitive ability may have been affected by a brain tumor.

5.10 Risk Factors/Possible Preventions

The exact cause(s) of brain tumors is/are currently still being investigated through ongoing research. Pursuant to study information gathered so far, it appears that exposure to ionizing radiation from high-intensity X-rays or other sources can damage brain cells and possibly lead to the formation of brain tumors such as

meningiomas or gliomas. Family history does not appear to be a significant factor, as the development of brain tumors within same-family relatives is very rare.

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6

Breast Cancer

6.1 Introduction

Breast cancer is one of the most common invasive cancers in women. In fact, it is the second leading cause of cancer death in women, after lung cancer. Although mainly female cancer, it has been seen in males, though very rarely. Breast cancer occurs when cells in the breast start to grow out of control, forming a tumor that can be seen on X-ray or felt as a lump (Figure 6.1). The tumor may be malignant if the cells can grow into surrounding tissues and spread to nearby organs or other areas of the body [1–144].

6.2 Genes Associated with Breast Cancer (Pathophysiology)

The mutation of BRCA1 or BRCA2 gene is the most common cause of hereditary breast cancer [4]. Scientists believe that gene mutations affecting biophysiological cell regulation pathways (called the *PI-3K-AKT-mTOR* and *RAS/MEK/ERK pathways*) are mainly responsible for breast cancer, although several other genes are also involved including *ATM*, *TP53*, *CHEK-2*, *PTEN*, *CDH1*, *STK11*, and *PLB2* [5].

6.3 Describing Breast Cancer

Breast cancer is categorized according to the size of the tumor and whether it has spread (metastasized) to lymph nodes or other distant parts of the body. There are different ways of staging breast cancer. Major stages are 0 through 4, but these may be broken down into smaller stages (Figure 6.2).

Stage 0: Known as ductal carcinoma in situ (DCIS), cancerous cells are limited to within a duct and have not invaded surrounding tissues.

Stage 1: At the beginning of this stage, the tumor is up to 2 centimeters (cm) across in size; it has not affected any lymph nodes.

Stage 2: The tumor is 2 cm across, and it has begun to spread to nearby nodes.

Stage 3: The tumor is up to 5 cm across and may have spread to some lymph nodes.

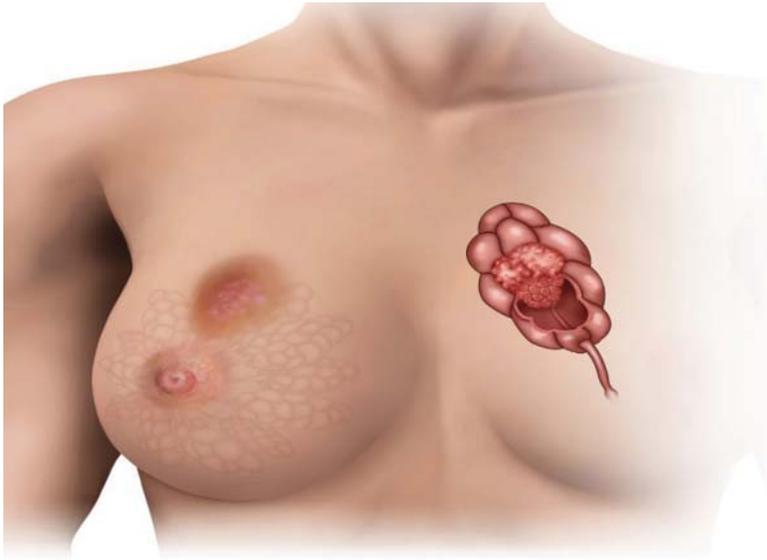


Figure 6.1 Tumor formation at a breast duct.

Stages of breast cancer

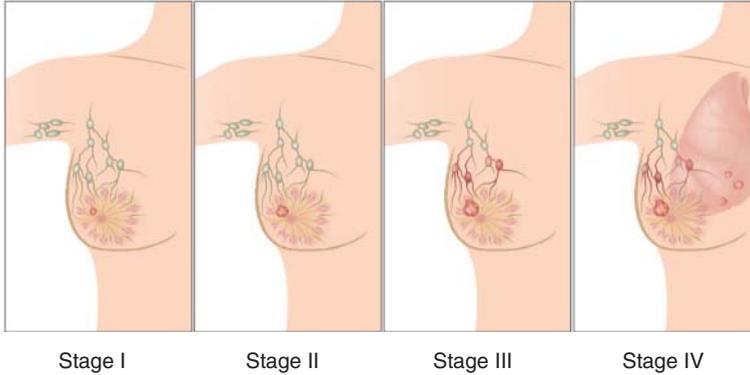


Figure 6.2 Scheme depicting breast cancer stages.

Stage 4: Cancer has spread to distant organs, particularly the bones, liver, brain, or lungs.

Breast cancer is further described by type. **Ductal carcinoma**, the most common type, begins in the milk duct. **Lobular carcinoma** starts in the lobules.

Breast cancer is called **invasive** when the cancer cells break out from inside the lobules or ducts and invade nearby tissue or spread to other parts of the body. **Noninvasive** breast cancer means the cancer cells are still at their place of origin and have not broken outside the duct or lobule. Nevertheless, these cells may eventually develop into invasive breast cancer.

6.4 Breast Cancer Symptoms

Palpable breast lumps (most lumps are not cancerous, but women should check with a medical specialist) (Based on [2–8])

- Pain in the underarm, breast, or nipples, which does not change with the monthly cycle
- Breast skin redness
- Rash around or on one of the nipples
- Discharge from a nipple with blood
- Sunken or inverted nipple (turning inward)
- Change in size or shape of the breast
- Peeling, flaking, or scaling of the skin on the breast or nipple
- Skin irritation that resembles the texture of an orange peel

6.5 Diagnosis

Breast cancer is detected and identified through a variety of means [22–30].

6.5.1 Breast Examination

A breast self-exam can be done at home, to detect the presence of lumps in or around the breast. A physician performs this during an examination, also checking for any additional symptoms.

6.5.2 Imaging Tests

A **mammogram** is a type of X-ray generally used for initial breast cancer screening. The images help trained specialists detect any lumps or abnormalities. At times, an uncertain result necessitates that the patient repeats the mammogram. Although anxiety-provoking for the patient, it is best to be thorough in order to rule out the start of breast cancer. An **ultrasound** scan can aid in differentiating between a solid mass and a fluid-filled cyst, which is not a tumor. An **MRI** scan involves injecting a dye into the patient; this type of radiodiagnostic test can show if or to what extent cancer cells have spread.

6.5.3 Biopsy

A sample of tissue is surgically removed for laboratory analysis to determine whether the cells are cancerous, and, if so, which type of cancer it is. A biopsy can also provide information on whether or not the cancer is hormone-sensitive.

Diagnosis also involves **staging** the breast cancer, as described above, to establish a better understanding of its nature and extent, in order to determine a patient's chances of recovery and the most effective treatment option.

6.6 Methods of Treatment

Breast cancer treatment depends on the type and stage of the condition, as well as its sensitivity to hormones. Other factors include the patient's age, overall health, and treatment preferences. The main options are surgery, radiation therapy, chemotherapy, hormone therapy, targeted drug therapy, and immunotherapy [25, 31–198].

6.6.1 Surgery

If surgery is required to remove the tumor, the choices in this regard depend on the diagnosis and the details of each individual's case.

6.6.1.1 Lumpectomy

Removing the tumor and a small margin of healthy tissue around it can help prevent the further spreading of cancer. This process is used if the tumor is small and likely easily separable from the surrounding tissue.

6.6.1.2 Mastectomy

General mastectomy involves the removal of the breast lobules, ducts, fatty tissue, nipple, areola, and some skin. In a radical mastectomy, all of the above tissues are removed, in addition to muscle from the chest wall and the underarm lymph nodes.

6.6.1.3 Sentinel Node Biopsy

In this procedure, the sentinel lymph node is located, extracted, and then biopsied to check for the presence of cancer cells. If none is found, this suggests that cancer has not developed the ability to spread to regions around it because the invasion of the lymph nodes is the way cancer is spread throughout the body via the lymphatic system.

6.6.1.4 Axillary Lymph Node Dissection

If cancer cells are found in the sentinel lymph node, a medical specialist may recommend removing several armpit lymph nodes to prevent the disease from spreading further.

6.6.1.5 Reconstruction

Following breast cancer surgery on one breast only, physicians can recommend a reconstruction procedure involving the unaffected breast, so that both breasts appear similar. Undergoing reconstruction is the patient's choice. The surgeon may use a breast implant or tissue from another part of the patient's body as material for reconstruction.

6.6.2 Radiation Therapy

After the tumor is removed, controlled radiation is targeted at the tumor site to destroy any remaining cancer cells.

6.6.3 Chemotherapy

Specialized drugs are used to kill cancer cells if there is a high risk of cancer spreading or recurring. Chemotherapy can involve the use of a combination of two or three drugs. Some treatment drugs are designed specifically to reduce estrogen production, as estrogen can enhance the growth of some breast cancers. Currently, 5-fluorouracil (5-FU), capecitabine (Xeloda), carboplatin (Paraplatin), paclitaxel (Taxol), docetaxel (Taxotere), albumin-bound paclitaxel (Abraxane), doxorubicin (Adriamycin), epirubicin (Ellence), cyclophosphamide (Cytoxan), carboplatin (Paraplatin), vinorelbine (Navelbine), gemcitabine (Gemzar), ixabepilone (Ixempra), eribulin (Halaven), methotrexate sodium (Trexall), thiotepa (Tepadina), and vinblastine sulfate are used to treat breast cancer or a combination of two or three drugs of these are used.

Adverse effects from chemotherapy include nausea, vomiting, loss of appetite, fatigue, sore mouth, hair loss, and possible infections. However, other medications can help control many of these symptoms.

6.6.4 Hormone-Blocking Therapy

Specialized drugs are used to prevent recurrence in hormone-sensitive breast cancers. The latter are often referred to as ER-positive (ER = estrogen receptor) and PR-positive (PR = progesterone receptor) cancers. Anastrozole (Arimidex), exemestane (Aromasin), fulvestrant (Faslodex), letrozole (Femara), megestrol acetate (Megace), tamoxifen (Nolvadex), and toremifene (Fareston) are used to treat breast cancer.

6.6.5 Targeted Therapy

Targeted drugs kill specific types of breast cancers, which are caused by specific gene mutations. Examples include lapatinib (Tykerb), neratinib (Nerlynx), tucatinib (Tukysa), palbociclib (Ibrance), ribociclib (Kisqali), abemaciclib (Verzenio), everolimus (Afinitor), and alpelisib (Piqray) as kinase inhibitors; olaparib (Lynparza) and talazoparib (Talzenna) as PARP inhibitors; bevacizumab (Avastin), margetuximab-cmkb (Margenza), and pertuzumab (Perjeta) as monoclonal antibodies; ado-trastuzumab (Herceptin), fam-trastuzumab deruxtecan (Enhertu), and sacituzumab govitecan (Trodelvy) as antibody drug-conjugates; fulvestrant (Faslodex) as a selective estrogen receptor degrader; goserelin (Zoladex) as a gonadotropin-releasing hormone agonist, and some other classes of drugs are available in the market.

6.6.6 Immunotherapy

PD-1 inhibitor pembrolizumab (Keytruda) and PD-L1 inhibitor atezolizumab (Tecentriq) are used to treat breast cancer.

6.6.7 Abbreviations for a Chemotherapy Combination Used to Treat Breast Cancer

AC

A = Doxorubicin (Adriamycin)

C = Cyclophosphamide

AT

A = Adriamycin

T = Taxotere

AC ± T with or without Taxol or Taxotere

A = Doxorubicin (Adriamycin)

C = Cyclophosphamide

T = Paclitaxel (Taxol)

CAF

C = Cyclophosphamide

A = Doxorubicin hydrochloride (Adriamycin)

F = Fluorouracil

CMF

C = Cyclophosphamide

M = Methotrexate

F = Fluorouracil

FEC

F = Fluorouracil

E = Epirubicin hydrochloride

C = Cyclophosphamide

TAC

T = Docetaxel (Taxotere)

A = Doxorubicin hydrochloride (Adriamycin)

C = Cyclophosphamide

6.6.8 Drugs to Prevent Breast Cancer

Raloxifene hydrochloride (Evista) and tamoxifen citrate (Soltamox) are used to prevent breast cancer.

6.7 Drugs for Breast Cancer in Men

Breast cancer occurs mainly in women. In rare cases, breast cancer can occur in men. Similar drugs can be used to treat breast cancer in men.

6.8 Treatment Regimens

Currently, several treatment regimens are available [25, 31–198].

6.8.1 Preoperative/Adjuvant Therapy Regimens for HER2-Negative Breast Cancer

AC

Doxorubicin: 60 mg/m² IV on day 1
 Cyclophosphamide: 600 mg/m² IV over 30 minutes on day 1
 Repeat cycle every three weeks for four cycles [81, 84].

AC→T (AC followed by Paclitaxel)

Doxorubicin: 60 mg/m² IV on day 1
 Cyclophosphamide: 600 mg/m² IV over 30 minutes on day 1
 Repeat cycle every three weeks for a total of four cycles, followed by
 Paclitaxel: 175 mg/m² IV over three hours on day 1
 Repeat cycle every three weeks for a maximum of four cycles [82]. All cycles are with myeloid growth factor support.

AC→T (weekly) (AC followed by weekly Paclitaxel)

Doxorubicin: 60 mg/m² IV on day 1
 Cyclophosphamide: 600 mg/m² IV over 30 minutes on day 1
 Repeat cycle every three weeks for four cycles with filgrastim support, followed by
 Paclitaxel: 80 mg/m² IV over one hour on day 1
 Repeat cycle weekly for a total of 12 cycles [82].

AC→Docetaxel (AC followed by Docetaxel)

Doxorubicin: 60 mg/m² IV on day 1
 Cyclophosphamide: 600 mg/m² IV over 30 minutes on day 1
 Repeat cycle every 21 days for four cycles with filgrastim support, followed by
 Docetaxel: 100 mg/m² IV over 60 minutes on day 1
 Repeat cycle every 21 days for four cycles [83].

AC→Docetaxel (AC followed by Docetaxel weekly)

Doxorubicin: 60 mg/m² IV on day 1
 Cyclophosphamide: 600 mg/m² IV over 30 minutes on day 1
 Repeat cycle every 21 days for a total of four cycles, followed by
 Docetaxel: 35 mg/m² IV over 30 minutes on day 1
 Repeat cycle every week for 12 weeks [147].

TC

Docetaxel: 75 mg/m² IV over 60 minutes on day 1
 Cyclophosphamide: 600 mg/m² IV over 30 minutes on day 1
 Repeat cycle every three weeks for four cycles [84, 147].

TAC

Doxorubicin (Adriamycin): 50 mg/m² IV infusion over 15 minutes on day 1
 Cyclophosphamide: 500 mg/m² IV over five minutes on day 1, then after
 a one-hour interval
 Docetaxel (Taxotere): 75 mg/m² IV over 60 minutes on day 1
 Repeat cycle every three weeks for up to six cycles [85].

CAF (FAC)

Doxorubicin (Adriamycin): 60 mg/m² IV over 15 minutes on day 1
 5-Fluorouracil: 600 mg/m² IV over 15 minutes on day 1
 Cyclophosphamide: 600 mg/m² IV over five minutes on day 1
 Repeat cycle every four weeks for four cycles [85, 148].

Cyclophosphamide + Methotrexate + 5-Fluorouracil (CMF)

Cyclophosphamide: 100 mg/m² orally once daily on days 1–14
 Methotrexate: 40 mg/m² IV weekly
 5-Fluorouracil: 600 mg/m² IV weekly
 Repeat cycle every four weeks for six cycles [86].

Epirubicin + CMF

Epirubicin: 100 mg/m² IV on day 1
 Repeat cycle every three weeks for four cycles, followed by
 Cyclophosphamide: 600 mg/m² IV over 30 minutes on day 1
 Methotrexate: 40 mg/m² IV on day 1
 5-Fluorouracil: 600 mg/m² IV on day 1
 Repeat cycle every 21 days for four cycles [87].

EC

Epirubicin: 100 mg/m² IV on day 1
 Cyclophosphamide: 830 mg/m² IV infusion over 30 minutes on day 1
 Repeat cycle every three weeks for a total of eight cycles [87].

5-Fluorouracil + Epirubicin + Cyclophosphamide (FEC)

5-Fluorouracil: 500 mg/m² IV on day 1
 Epirubicin: 100 mg/m² IV on day 1
 Cyclophosphamide: 500 mg/m² IV over 30 minutes on day 1
 Repeat cycle every 21 days for up to six cycles [149].

FEC + Docetaxel

5-Fluorouracil: 500 mg/m² IV on day 1
 Epirubicin: 100 mg/m² IV on day 1
 Cyclophosphamide: 500 mg/m² IV over 30 minutes on day 1
 Repeat cycle every 21 days for six cycles, followed by
 Docetaxel: 100 mg/m² IV over 60 minutes on day 1
 Repeat cycle every 21 days for a total of three cycles [150].

Capecitabine

1000–1250 mg/m² twice per day on days 1–14
 Repeat cycle every three weeks (two weeks on and one week off) [186].

Olaparib

300 mg orally twice daily on days 1–28
 Repeat cycle every 28 days and continue up to one year [187].

Paclitaxel + Carboplatin

Paclitaxel: 80 mg/m² IV infusion over one hour on days 1, 8, and 15
 Carboplatin: AUC of 1.5–2, IV over 30 minutes on days 1, 8, and 15
 Repeat cycle every 28 days for six cycles [188].

Dose-Dense Regimens for HER2-negative Disease**AC→T (Dose-dense AC followed by Paclitaxel)**

Doxorubicin: 60 mg/m² IV on day 1
 Cyclophosphamide: 600 mg/m² IV over 30 minutes on day 1
 Repeat cycle every 14 days for a total of four cycles, followed by
 Paclitaxel: 175 mg/m² IV over three hours on day 1
 Repeat cycle every 14 days for four cycles [82].
 Administer colony-stimulating factors supporting Peg-filgrastim (PEGylated filgrastim) 6 mg SC on day 2 of each treatment cycle.

Doxorubicin + Paclitaxel + Cyclophosphamide

Doxorubicin: 60 mg/m² IV on day 1
 Repeat cycle every 14 days for four cycles, followed by
 Paclitaxel: 175 mg/m² IV over three hours on day 1
 Repeat cycle every 14 days for a total of four cycles, followed by
 Cyclophosphamide: 600 mg/m² IV over 30 minutes on day 1
 Repeat cycle every 14 days for a total of four cycles [82].
 Administer colony-stimulating factors supporting Peg-filgrastim (PEGylated filgrastim) 5 µg/kg SC on days 3–10 of each cycle.

AC→Docetaxel (Dose-dense AC followed by Docetaxel)

Doxorubicin: 60 mg/m² IV on day 1
 Cyclophosphamide: 600 mg/m² IV over 30 minutes on day 1
 Repeat cycle every 14 days for four cycles, followed by
 Docetaxel: 75 mg/m² IV over 60 minutes on day 1
 Repeat cycle every 14 days for four cycles [88].
 Administer colony-stimulating factors supporting Peg-filgrastim (PEGylated filgrastim) 6 mg SC on day 2 of each treatment cycle.

6.8.2 Preoperative/Adjuvant Therapy Regimens for HER2-Positive Breast Cancer**AC→T + Trastuzumab (AC followed by Paclitaxel + Trastuzumab)**

Doxorubicin: 60 mg/m² IV on day 1
 Cyclophosphamide: 600 mg/m² IV over 30 minutes on day 1
 Repeat cycle every 21 days for a maximum of four cycles, followed by
 Paclitaxel: 80 mg/m² IV over one hour on day 1
 Trastuzumab: 4 mg/kg IV over 90 minutes of the first dose, then 2 mg/kg IV over 30 minutes weekly
 Repeat cycle every seven days for 12 cycles (12 weeks), followed by
 Trastuzumab: 2 mg/kg IV over 30 minutes weekly
 Repeat weekly for 40 weeks [25].

AC→T + Trastuzumab (Dose-dense AC followed by Paclitaxel + Trastuzumab)

Doxorubicin: 60 mg/m² IV on day 1
 Cyclophosphamide: 600 mg/m² IV over 30 minutes on day 1
 Repeat cycle every 14 days for four cycles, followed by
 Paclitaxel: 175 mg/m² IV infusion over three hours on day 1
 Trastuzumab: 4 mg/kg IV over 90 minutes with the first dose of paclitaxel, then 2 mg/kg IV over 30 minutes weekly
 Repeat cycle weekly for 12 weeks, followed by
 Trastuzumab: 2 mg/kg IV infusion over 30 minutes weekly
 Repeat weekly for 40 weeks [89].

Paclitaxel + Trastuzumab

Paclitaxel: 80 mg/m² IV infusion over one hour weekly for 12 weeks
 Trastuzumab: 4 mg/kg IV with the first dose of paclitaxel on week 1, then 2 mg/kg weekly for 11 weeks, after 12 weeks
 Trastuzumab dose is 6 mg/kg every three weeks for 40 weeks [189].

AC followed by Paclitaxel + Trastuzumab + Pertuzumab

Doxorubicin: 60 mg/m² IV on day 1
 Cyclophosphamide: 600 mg/m² IV on day 1
 Repeat cycle every 21 days for a total of four cycles, followed by
 Pertuzumab: 840 mg IV infusion over one hour on day 1 for cycle 1, then
 420 mg IV infusion over 30 minutes for cycles 2–4
 Trastuzumab: 8 mg/kg IV infusion over 90 minutes on day 1 for cycle 1,
 then 6 mg/kg IV for cycles 2–4, followed by
 Paclitaxel: 80 mg/m² IV on days 1, 8, and 15
 Repeat cycle every 21 days for four cycles, followed by
 Trastuzumab: 6 mg/kg IV on day 1
 Pertuzumab: 420 mg IV on day 1
 Repeat cycle every 21 days to complete one-year therapy for trastuzumab and
 pertuzumab [25].

Docetaxel + Trastuzumab + 5-Fluorouracil + Epirubicin + Cyclophosphamide

Docetaxel: 100 mg/m² IV infusion over 60 minutes on day 1
 Trastuzumab (Herceptin): 4 mg/kg IV over 90 minutes loading dose on day 1,
 then 2 mg/kg IV over 30 minutes weekly
 Repeat cycle every 21 days for three cycles, followed by
 5-Fluorouracil: 600 mg/m² IV on day 1
 Epirubicin: 60 mg/m² IV on day 1
 Cyclophosphamide: 600 mg/m² IV over 30 minutes on day 1
 Repeat cycle every 21 days for a total of three cycles. [90].

Docetaxel + Pertuzumab + Trastuzumab

Docetaxel: 75 mg/m² IV over 60 minutes on day 1
 Trastuzumab: 8 mg/kg IV over 90 minutes' loading dose on day 1, then
 6 mg/kg IV over 30 minutes every three weeks
 Pertuzumab: 840 mg IV over 60 minutes' loading dose on day 1, then
 420 mg IV over 30 minutes every three weeks
 Repeat cycle every 21 days [192].

TCH

Docetaxel: 75 mg/m² IV over 60 minutes on day 1
 Carboplatin: AUC of 6, IV over 30 minutes on day 1
 Trastuzumab: 4 mg/kg IV over 90 minutes' loading dose, then 2 mg/kg IV
 over 30 minutes weekly
 Repeat cycle every three weeks for six cycles. After six cycles, administer
 trastuzumab as monotherapy at a dose of 6 mg/kg every three weeks to complete
 one year of trastuzumab treatment therapy [91].

TCH + Pertuzumab

Docetaxel: 75 mg/m² IV over 60 minutes on day 1

Carboplatin: AUC of 6, IV over 30 minutes on day 1

Trastuzumab: 8 mg/kg IV on day 1

Pertuzumab: 840 mg IV on day 1

Repeat cycle every three weeks for six cycles, followed by

Trastuzumab: 6 mg/kg IV on day 1

Pertuzumab: 420 mg IV on day 1

Repeat cycle every 21 days to complete one year of trastuzumab and pertuzumab therapy [146].

Neratinib

240 mg orally once daily for one year following adjuvant trastuzumab-containing therapy for patients with hormone receptor-positive [41].

Ado-trastuzumab Emtansine

3.6 mg/kg IV on day 1

Repeat cycle every three weeks for up to 14 cycles [92].

6.8.3 Systemic Therapy for ER- and/or PR-Positive Recurrent or Stage IV (M1) Disease: HER2-Negative and Postmenopausal or Premenopausal Receiving Ovarian Ablation or Suppression**Abemaciclib + Anastrozole**

Abemaciclib: 150 mg orally twice daily on days 1–28

Anastrozole: 1 mg orally once daily on days 1–28

Repeat cycle every 28 days [97, 117].

Abemaciclib + Exemestane

Abemaciclib: 150 mg orally twice daily on days 1–28

Exemestane: 25 mg orally once daily on days 1–28

Repeat cycle every 28 days [155].

Abemaciclib + Fulvestrant

Abemaciclib: 150 mg orally twice daily on days 1–28

Fulvestrant: 500 mg IM on days 1 and 15 of the first cycle and then 500 mg IM monthly for all subsequent cycles

Repeat cycle every four weeks [94].

Abemaciclib + Letrozole

Abemaciclib: 150 mg orally twice daily on days 1–28

Letrozole: 2.5 mg orally once daily on days 1–28

Repeat cycle every 28 days [117].

Fulvestrant + Anastrozole

Fulvestrant: 500 mg IM on days 1 and 15 of the first cycle and then 500 mg IM monthly for all subsequent cycles

Anastrozole: 1 mg orally once daily on days 1–28

Repeat cycle every four weeks [94, 98].

Fulvestrant + Letrozole

Fulvestrant: 500 mg IM on days 1 and 15 of the first cycle and then 500 mg IM monthly for all subsequent cycles

Letrozole: 2.5 mg orally once daily on days 1–28

Repeat cycle every four weeks [98].

Palbociclib + Anastrozole

Palbociclib: 125 mg orally once daily on days 1–21

Anastrozole: 1 mg orally once daily on days 1–28

Repeat cycle every four weeks [99].

Palbociclib + Exemestane

Palbociclib: 125 mg orally once daily on days 1–21

Exemestane: 25 mg orally once daily on days 1–28

Repeat cycle every four weeks [99].

Palbociclib + Fulvestrant

Palbociclib: 125 mg orally once daily on days 1–21

Fulvestrant: 500 mg IM on days 1 and 15 of the first cycle and then 500 mg IM monthly for all subsequent cycles

Repeat cycle every four weeks [158].

Palbociclib + Letrozole

Palbociclib: 125 mg orally once daily on days 1–21

Letrozole: 2.5 mg orally once daily on days 1–28

Repeat cycle every four weeks [99].

Ribociclib + Anastrozole

Ribociclib: 600 mg orally once daily on days 1–21

Anastrozole: 1 mg orally once daily on days 1–28

Repeat cycle every four weeks [100].

Ribociclib + Exemestane

Ribociclib: 600 mg orally once daily on days 1–21

Exemestane: 25 mg orally once daily on days 1–28

Repeat cycle every four weeks [159].

Ribociclib + Fulvestrant

Ribociclib: 600 mg orally once daily on days 1–21

Fulvestrant: 500 mg IM on days 1 and 15 of the first cycle and then 500 mg IM monthly for all subsequent cycles

Repeat cycle every four weeks [101].

Ribociclib + Letrozole

Ribociclib: 600 mg orally once daily on days 1–21

Letrozole: 2.5 mg orally once daily on days 1–28

Repeat cycle every four weeks [100].

Alpelisib + Fulvestrant

Alpelisib: 300 mg orally once daily on days 1–28

Fulvestrant: 500 mg IM on days 1, 15, and 29

Repeat cycle every four weeks [102].

Everolimus + Exemestane

Everolimus: 10 mg orally once daily on days 1–28

Exemestane: 25 mg orally once daily on days 1–28

Repeat cycle every four weeks [40, 160].

Everolimus + Fulvestrant

Everolimus: 10 mg orally once daily on days 1–28

Fulvestrant: 500 mg IM on days 1 and 15 of the first cycle and then 500 mg IM monthly for all subsequent cycles

Repeat cycle every four weeks [103].

Everolimus + Tamoxifen

Everolimus: 10 mg orally once daily on days 1–28

Tamoxifen: 25 mg orally once daily on days 1–28

Repeat cycle every four weeks [40, 160].

Abemaciclib

200 mg orally twice daily on days 1–28

Repeat cycle every 28 days [123].

Anastrozole

1 mg orally once daily on days 1–28

Repeat cycle every 28 days [94].

Exemestane

25 mg orally once daily on days 1–28
Repeat cycle every 28 days [132].

Fulvestrant

250 mg IM on day 1
Repeat cycle every four weeks [182].

Letrozole

2.5 mg orally once daily on days 1–28
Repeat cycle every 28 days [135].

Megestrol

40 mg orally four times daily on days 1–28
Repeat cycle every 28 days [136].

Tamoxifen

20 mg orally once daily on days 1–28
Repeat cycle every 28 days [142].

Toremifene

60 mg orally once daily on days 1–28
Repeat cycle every 28 days [143].

Estradiol

6–30 mg orally once daily on days 1–28
Repeat cycle every four weeks [197].

6.8.4 Systemic Therapy Regimens for Recurrent/Unresectable/ Advanced/Metastatic Stage IV Breast Cancer: Regimens for HER2-Negative Disease

AC

Doxorubicin: 60 mg/m² IV on day 1
Cyclophosphamide: 600 mg/m² IV over 30 minutes on day 1
Repeat cycle every three weeks [153].

AT

Doxorubicin: 60 mg/m² IV on day 1
Paclitaxel: 150 mg/m² IV over 24 hours on day 1
Repeat cycle every three weeks [154].

EC

Epirubicin: 75 mg/m² IV as a bolus or short infusion on day 1
 Cyclophosphamide: 600 mg/m² IV as a bolus or short infusion on day 1
 Repeat cycle every 21 days [191].

Gemcitabine + Paclitaxel (GT)

Gemcitabine: 1250 mg/m² IV over 30 minutes on days 1 and 8
 Paclitaxel: 175 mg/m² IV over three hours on day 1
 Repeat cycle every 21 days [164].

Capecitabine + Docetaxel

Capecitabine: 1000–1250 mg/m² orally twice daily on days 1–14
 Docetaxel: 75 mg/m² IV over 60 minutes on day 1
 Repeat cycle every three weeks [161].

Capecitabine + Ixabepilone

Capecitabine: 1000 mg/m² orally twice daily on days 1–14
 Ixabepilone: 40 mg/m² IV over three hours on day 1
 Repeat cycle every 21 days [162].

Capecitabine + Paclitaxel

Capecitabine: 825 mg/m² orally twice daily on days 1–14
 Paclitaxel: 175 mg/m² IV over three hours on day 1
 Repeat cycle every 21 days [193].

Carboplatin + Paclitaxel

Paclitaxel: 200 mg/m² IV infusion over three hours on day 1
 Carboplatin: AUC of 6, IV infusion over 30 minutes on day 1
 Repeat cycle every 21 days [165, 166].

Paclitaxel + Bevacizumab

Paclitaxel: 90 mg/m² IV infusion over 60 minutes on days 1, 8, and 15
 Bevacizumab: 10 mg/kg IV infusion over 30–90 minutes on days 1 and 15
 Repeat cycle every four weeks [104].

Atezolizumab + Albumin-Bound Paclitaxel

Atezolizumab: 840 mg IV infusion over 60 minutes on days 1 and 15
 Albumin-bound Paclitaxel: 100 mg/m² IV infusion over 60 minutes on days 1, 8,
 and 15
 Repeat cycle every four weeks [42].

Docetaxel + Doxorubicin

Docetaxel: 75 mg/m² IV over 60 minutes on day 1

Doxorubicin: 50 mg/m² IV on day 1

Repeat cycle every three weeks [153, 167].

Doxorubicin liposomal + Docetaxel

Doxorubicin liposome: 30 mg/m² IV infusion on over 60 minutes on day 1,
followed by after 1 hour

Docetaxel: 60 mg/m² IV over 60 minutes on day 1

Repeat cycle every three weeks and continue until disease progression or prohibitive toxicity [168].

CEF

Cyclophosphamide: 75 mg/m² orally once daily on days 1–14

Epirubicin: 60 mg/m² IV on days 1 and 8

5-Fluorouracil: 500 mg/m² IV over 30 minutes on days 1 and 8

Repeat cycle every 28 days [169].

CMF

Cyclophosphamide: 100 mg/m² orally once daily on days 1–14

Methotrexate: 40 mg/m² IV on days 1 and 8

5-Fluorouracil: 500 mg/m² IV over 30 minutes on days 1 and 8

Repeat cycle every four weeks [105, 169].

FEC-75

5-Fluorouracil: 500 mg/m² IV over 30 minutes on day 1

Epirubicin: 75 mg/m² IV on day 1

Cyclophosphamide: 500 mg/m² IV over 30 minutes on day 1

Repeat cycle every 21 days [171].

FEC-50

5-Fluorouracil: 500 mg/m² IV over 30 minutes on day 1

Epirubicin: 50 mg/m² IV on day 1

Cyclophosphamide: 500 mg/m² IV over 30 minutes on day 1

Repeat cycle every 21 days [171].

Albumin-bound paclitaxel

260 mg/m² IV over 30 minutes on day 1

Repeat cycle every 21 days [124].

Cyclophosphamide

50 mg/m² IV over 30 minutes on day 1
Repeat cycle every 21 days [176].

Docetaxel

60–100 mg/m² IV over 60 minutes on day 1
Repeat cycle every 21 days
Or 35 mg/m² IV over 30 minutes weekly [127, 196].

Doxorubicin

20 mg/m² IV on day 1
Repeat cycle every seven days
Or 60–75 mg/m² IV infusion over 60 minutes on day 1
Repeat cycle every 21 days [128, 190].

Doxorubicin liposome

40–50 mg/m² IV infusion over 60 minutes on day 1
Repeat cycle every 28 days [129].

Eribulin

1.4 mg/m² IV over five minutes on days 1 and 8
Repeat cycle every 21 days [114, 137].

Gemcitabine

800–1200 mg/m² IV over 30 minutes on days 1, 8, and 15
Repeat cycle every 28 days [183].

Ixabepilone

40 mg/m² IV infusion over three hours on day 1
Repeat cycle every 21 days [112].

Paclitaxel

175 mg/m² IV over three hours on day 1
Repeat cycle every 21 days [138].
Or
80–100 mg/m² IV infusion over one hour weekly for three weeks
Repeat cycle every four weeks [139].

Vinorelbine

25–30 mg/m² IV over 5–10 minutes on day 1
Repeat cycle every seven days [137, 144].

6.8.5 Systemic Therapy for ER- and/or PR-Positive Recurrent or Stage IV (M1) Disease: Regimens for HER2-Positive Postmenopausal or Premenopausal Receiving Ovarian Ablation or Suppression

Trastuzumab + Anastrozole

Trastuzumab: 4 mg/kg IV loading dose on day 1, and then 2 mg/kg IV every seven days

Anastrozole: 1 mg orally once daily on days 1–7

Repeat cycle every seven days [172].

Trastuzumab + Fulvestrant

Trastuzumab: 4 mg/kg IV over 90 minutes loading dose on day 1 and then 2 mg/kg IV weekly

Fulvestrant: 500 mg IM on days 1 and 15 of the first cycle and then 500 mg IM on day 1 for all subsequent cycles

Repeat cycle every four weeks [111].

Trastuzumab + Letrozole

Trastuzumab: 4 mg/kg IV over 90 minutes' loading dose on day 1 and then 2 mg/kg IV weekly

Letrozole: 2.5 mg orally once daily on days 1–28

Repeat cycle every four weeks [106, 172].

Trastuzumab + Tamoxifen

Trastuzumab: 4 mg/kg IV over 90 minutes' loading dose on day 1 and then 2 mg/kg IV weekly

Tamoxifen: 20 mg orally once daily on days 1–28

Repeat cycle every four weeks [172].

Everolimus + Exemestane

Everolimus: 10 mg orally once daily on days 1–28

Exemestane: 25 mg orally once daily on days 1–28

Repeat cycle every 28 days [40].

Palbociclib + Letrozole

Palbociclib: 125 mg orally once daily on days 1–21

Letrozole: 2.5 mg orally once daily on days 1–21

Repeat cycle every 21 days [99].

Palbociclib + Fulvestrant

Palbociclib: 125 mg orally once daily on days 1–21

Fulvestrant: 500 mg IM on days 1 and 15 of the first cycle and then 500 mg IM on day 1 every month for all subsequent cycles

Repeat cycle every 28 days [116].

Ribociclib + Fulvestrant

Ribociclib: 600 mg orally once daily on days 1–21

Fulvestrant: 500 mg IM on days 1 and 15 of the first cycle and then 500 mg IM on day 1 in every month

Repeat cycle every four weeks (three weeks on, one week rest).

Abemaciclib + Anastrozole

Abemaciclib: 150 mg orally twice daily on days 1–28

Anastrozole: 1 mg orally once daily on days 1–28

Repeat cycle every 28 days [117].

Abemaciclib + Exemestane

Abemaciclib: 150 mg orally twice daily on days 1–28

Exemestane: 25 mg orally once daily on days 1–28

Repeat cycle every 28 days.

Abemaciclib + Fulvestrant

Abemaciclib: 150 mg orally twice daily on days 1–28

Fulvestrant: 500 mg IM on days 1 and 15 of the first cycle and then 500 mg IM on day 1 for all subsequent cycles

Repeat cycle every four weeks [179].

Abemaciclib + Letrozole

Abemaciclib: 150 mg orally twice daily on days 1–28

Letrozole: 2.5 mg orally once daily on days 1–28

Repeat cycle every four weeks [117].

Exemestane + Lapatinib

Exemestane: 25 mg orally once daily on days 1–28

Lapatinib: 1500 mg orally once daily on days 1–28

Repeat cycle every four weeks [122, 155].

Letrozole + Lapatinib

Letrozole: 2.5 mg orally once daily on days 1–28

Lapatinib: 1500 mg orally once daily on days 1–28

Repeat cycle every four weeks [118].

Goserelin + Anastrozole + Zoledronic acid

Goserelin: 3.6 mg SC every 28 days

Anastrozole: 1 mg orally once daily

Zoledronic acid: 4 mg IV infusion over 15 minutes every six months

Continue regimens for a maximum of three years [152].

Goserelin + Tamoxifen + Zoledronic acid

Goserelin: 3.6 mg SC every 28 days
Tamoxifen: 20 mg orally once daily
Zoledronic acid: 4 mg IV infusion over 15 minutes every six months
Continue regimens up to three years [152].

Abemaciclib

200 mg orally twice daily on days 1–28
Repeat cycle every 28 days [123].

Anastrozole

1 mg orally once daily on days 1–28
Repeat cycle every 28 days [94].

Exemestane

25 mg orally once daily on days 1–28
Repeat cycle every 28 days [132].

Fulvestrant

250 mg IM on day 1
Repeat cycle every four weeks [182].

Letrozole

2.5 mg orally once daily on days 1–28
Repeat cycle every 28 days [135].

Megestrol

40 mg orally four times daily on days 1–28
Repeat cycle every 28 days [136].

Tamoxifen

20 mg orally once daily on days 1–28
Repeat cycle every 28 days [142].

Toremifene

60 mg orally once daily on days 1–28
Repeat cycle every 28 days [143].

6.8.6 Systemic Therapy Regimens for Recurrent/Unresectable/Advanced/Metastatic Stage IV Breast Cancer: Regimens for HER2-Positive Disease

Trastuzumab + Capecitabine

Trastuzumab: 4 mg/kg IV over 90 minutes' loading dose and then 2 mg/kg IV weekly

Capecitabine: 1250 mg/m² orally twice daily on days 1–14

Repeat cycle every 21 days [194].

Trastuzumab + Gemcitabine

Trastuzumab: 4 mg/kg IV infusion over 90 minutes' loading dose and then 2 mg/kg IV weekly

Gemcitabine: 800–1200 mg/m² IV over 30 minutes on days 1, 8, and 15

Repeat cycle every 21 days [195].

Trastuzumab + Docetaxel

Trastuzumab: 4 mg/kg IV loading dose on day 1 and then 2 mg/kg IV on days 8 and 15

Docetaxel: 35 mg/m² IV over 60 minutes on days 1, 8, and 15

Repeat cycle every 28 days (three weeks on/one week off) [173].

Trastuzumab + Paclitaxel

Trastuzumab: 4 mg/kg IV over 90 minutes' loading dose on day 1 and then 2 mg/kg IV weekly

Paclitaxel: 90 mg/m² IV over one hour on day 1

Repeat cycle every seven days [108].

Trastuzumab + Lapatinib

Trastuzumab: 4 mg/kg IV loading dose on day 1 and then 2 mg/kg IV weekly

Lapatinib: 1000 mg orally once daily on days 1–21

Repeat cycle every three weeks [109, 110].

Trastuzumab + Navelbine

Trastuzumab: 4 mg/kg IV over 90 minutes' loading dose on day 1 and then 2 mg/kg IV weekly

Navelbine: 25 mg/kg IV weekly

Repeat cycle every one week [174].

Trastuzumab + Carboplatin

Trastuzumab: 4 mg/kg IV over 90 minutes' loading dose on day 1 and then 2 mg/kg IV over 30 minutes weekly

Carboplatin: AUC of 6, IV over 30 minutes on day 1

Repeat cycle every three weeks.

Trastuzumab + Cisplatin

Trastuzumab: 4 mg/kg IV over 90 minutes' loading dose on day 1 and then
2 mg/kg IV over 30 minutes weekly

Cisplatin: 75 mg/m² IV over 60 minutes on day 1

Repeat cycle every three weeks [107].

Trastuzumab + Cyclophosphamide

Trastuzumab: 4 mg/kg IV over 90 minutes' loading dose on day 1 and then
2 mg/kg IV over 30 minutes weekly

Cyclophosphamide: 50 mg orally once daily on days 1–21

Repeat cycle every three weeks [107].

Trastuzumab + Eribulin

Trastuzumab: 4 mg/kg IV over 90 minutes' loading dose on day 1 and then
2 mg/kg IV over 30 minutes weekly

Eribulin: 1.4 mg/m² IV on days 1 and 8

Repeat cycle every three weeks [107, 114].

Trastuzumab + Vinorelbine

Trastuzumab: 4 mg/kg IV on day 1 and then 2 mg/kg IV weekly

Vinorelbine: 25 mg/m² IV on day 1

Repeat cycle every three weeks [177].

Capecitabine + Lapatinib

Capecitabine: 1000 mg/m² orally twice daily on days 1–14

Lapatinib: 1000 mg orally once daily on days 1–21

Repeat cycle every 21 days [115].

Capecitabine + Neratinib

Capecitabine: 750 mg/m² orally twice daily on days 1–14

Neratinib: 240 mg orally once per day on days 1–21

Repeat cycle every 21 days [178].

Docetaxel + Trastuzumab + Pertuzumab

Docetaxel: 75 mg/m² IV over 60 minutes on day 1

Trastuzumab: 8 mg/kg IV loading dose on day 1 and then 6 mg/kg
IV weekly

Pertuzumab: 840 mg IV loading dose on day 1 and then 420 mg IV every
three weeks

Repeat cycle every three weeks [119].

Pertuzumab + Trastuzumab + Paclitaxel

Pertuzumab: 840 mg IV loading dose on day 1 and then 420 mg IV every three weeks
 Trastuzumab: 8 mg/kg IV loading dose on day 1 and then 6 mg/kg IV weekly
 Paclitaxel: 80 mg/kg IV over 80 minutes on days 1, 8, and 15
 Repeat cycle every three weeks [120].

Paclitaxel + Carboplatin + Trastuzumab

Paclitaxel: 175 mg/kg IV over three hours on day 1
 Carboplatin: AUC of 6, IV over 30 minutes on day 1
 Trastuzumab: 4 mg/kg IV loading dose on day 1 and then 2 mg/kg IV weekly
 Repeat cycles every 21 days [121].

Carboplatin + Docetaxel + Trastuzumab

Carboplatin: AUC of 6, IV over 30 minutes on day 1
 Docetaxel: 75 mg/m² IV over 60 minutes on day 1
 Trastuzumab: 4 mg/kg IV over 90 minutes' loading dose on day 1 and then 2 mg/kg IV over 60 weekly
 Repeat cycle every three weeks [180].

Tucatinib + Trastuzumab + Capecitabine

Tucatinib: 300 mg orally twice daily on days 1–21
 Trastuzumab: 8 mg/kg IV loading dose on day 1, then 6 mg/kg IV once every three weeks
 Capecitabine: 1000 mg/m² orally twice daily on days 1–21
 Repeat cycle every 21 days [70].

Gemcitabine + Carboplatin + Trastuzumab

Gemcitabine: 1500 mg/m² IV over 30 minutes on day 1
 Carboplatin: AUC of 2.5, IV over 30 minutes on day 1
 Trastuzumab: 8 mg/kg IV loading dose on day 1 and then 4 mg/kg IV once every two weeks
 Repeat cycle every two weeks [181].

Margetuximab-cmkb + Capecitabine

Margetuximab-cmkb: 15 mg/kg IV infusion over two hours on day 1, given second
 Capecitabine: 1000 mg/m² orally twice daily on days 1–14, followed by seven days off
 Repeat cycle every 21 days [198].

Margetuximab-cmkb + Eribulin

Margetuximab-cmkb: 15 mg/kg IV infusion over two hours on day 1, given second
 Eribulin: 1.4 mg/m² IV on days 1 and 8, followed by seven days off
 Repeat cycle every 21 days [198].

Margetuximab-cmkb + Gemcitabine

Margetuximab-cmkb: 15 mg/kg IV infusion over two hours on day 1, given second
 Gemcitabine: 1000 mg/m² IV on days 1 and 8, followed by seven days off
 Repeat cycle every 21 days [198].

Margetuximab-cmkb + Vinorelbine

Margetuximab-cmkb: 15 mg/kg IV infusion over two hours on day 1, given second
 Vinorelbine: 25–30 mg/m² IV on days 1 and 8, followed by seven days off
 Repeat cycle every 21 days [198].

Ado-trastuzumab Emtansine

3.6 mg/kg IV on day 1
 Repeat cycle every 21 days [125].

Capecitabine

1000–1250 mg/m² orally twice daily on days 1–14
 Repeat cycle every 21 days [126].

Entrectinib (*NTRK* gene fusion-positive)

600–800 mg orally once daily on days 1–28
 Repeat cycle every 28 days [130].

Larotrectinib (*NTRK* gene fusion-positive)

100 mg orally twice daily on days 1–28
 Repeat cycle every four weeks [134].

Olaparib

300 mg orally twice daily on days 1–28
 Repeat cycle every 28 days [137].

Pembrolizumab

200 mg IV over 30 minutes on day 1
Repeat cycle every 21 days [140].

Sacituzumab govitecan-hziy

10 mg/kg IV on days 1 and 8
Repeat cycle every 21 days [67].

Talazoparib

1 mg orally once daily continuously with or without food on days 1–21
Repeat cycle every three weeks [141].

Trastuzumab

8 mg/kg IV over 90 minutes' loading dose on day 1 and then 6 mg/kg IV over 60 minutes every three weeks and continue until disease progression.

Or

4 mg/kg IV infusion over 90 minutes' loading dose on day 1 and then 2 mg/kg IV over 60 minutes weekly

Repeat cycle every week for a total of 10 weeks [184].

Fam-Trastuzumab Deruxtecan-nxki

5.4 mg or 6.4 mg/kg IV on day 1
Repeat cycle every 21 days [71].

Ado-trastuzumab emtansine

3.6 mg/kg IV on day 1
Repeat cycle every 21 days [125].

6.9 Risk Factors/Possible Preventions

The exact cause of breast cancer continues to be under ongoing research. Certain risk factors, many of which are preventable, are linked to a greater chance of developing the disease [9–21].

- (a) **Age:** The risk of developing breast cancer increases with age, with older individuals more frequently affected.
- (b) **Genetics:** If a close relative has or has had breast cancer, the risk of developing it is higher for family members. Women with the *BRCA1* and *BRCA2* genes have a higher risk of developing breast cancer, ovarian cancer, or both. These genes can be inherited. *TP53* is another gene that has been linked to a greater chance of developing breast cancer.

- (c) **History of breast cancer or breast lumps:** Women who have had breast cancer before are more likely to have it again, compared with those who have no history of the disease. Having some types of benign or noncancerous breast lumps increases the chance of developing cancer later on. Examples include atypical ductal hyperplasia or lobular carcinoma in situ.
- (d) **Dense breast tissue:** Breast cancer is more likely to grow in higher-density breast tissue. Dense breast tissue is characterized by greater amounts of fibrous and glandular tissue than fat tissue.
- (e) **Estrogen exposure and breastfeeding:** Over a lifetime, the longer an individual's exposure to estrogen, the greater is the risk of breast cancer. Estrogen levels are higher during menstruation. Breastfeeding, especially for over one year after giving birth, decreases the chance of developing breast cancer, possibly because pregnancy followed by breastfeeding reduces exposure to estrogen.
- (f) **Body weight:** Women who are overweight or obese after menopause may have a higher risk of developing breast cancer, possibly due to higher levels of estrogen. High sugar intake may be another factor.
- (g) **Alcohol consumption:** Drinking large quantities of alcohol on a regular basis appears to play a significant role in developing breast cancer. Studies have shown that women who consume more than 3 drinks per day have a 1.5 times higher risk of having the disease than those who do not drink.
- (h) **Radiation exposure:** Undergoing radiation treatment for cancer other than breast cancer increases an individual's risk of getting breast cancer later in life.
- (i) **Hormone treatments:** Undertaking hormone replacement therapy (HRT) or being on oral birth control pills both increase estrogen levels, which is associated with a higher risk of developing breast cancer.
- (j) **Occupational hazards:** Scientists reported that exposure to certain carcinogens and endocrine disruptors, some of which are related to particular occupations, may be linked to breast cancer.
- (k) **Cosmetic implants:** Women who have had cosmetic breast implants (textured) have a slightly higher risk of developing anaplastic large cell lymphoma (BIA-ALCL), which is a very rare cancer of the immune system.

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7

Colorectal Cancer

7.1 Introduction

The large intestine, also called the colon, is involved in the final stages of digestion. It is a large tube that escorts waste from the body. The function of the large intestine is to get rid of food left over after the nutrients are removed from it, leaving bacteria and other material not utilized by the body (Figure 7.1).

Cancers of the colon and rectum, together called *colorectal cancer*, are the third most common type of cancer worldwide. The cells lining the colon, which normally replicate and grow as required for proper organ functionality, become mutated and begin reproducing in an out-of-control manner [1–86]. The growth of these abnormal cells can lead to structures within the colon called polyps (Figure 7.2).

7.2 Genes Associated with Colorectal Cancer

Colorectal cancers are believed to be associated possibly with mutations in the Wnt signaling pathway and *APC* gene, which produces APC protein. Other proteins responsible for colon cancers that are activated or deactivated are *KRAS*, *TGF- β* , *PI-3K*, *PTEN*, abnormal DNA methylation, and others [6–20].

7.3 Colorectal Cancer Symptoms

- Diarrhea or constipation
- Changes in stool consistency
- Loose and narrow stools
- Rectal bleeding or bloody stool
- Abdominal pain, cramps, bloating, or gas
- Pain during bowel movements
- Continual urge to defecate
- Weakness and fatigue

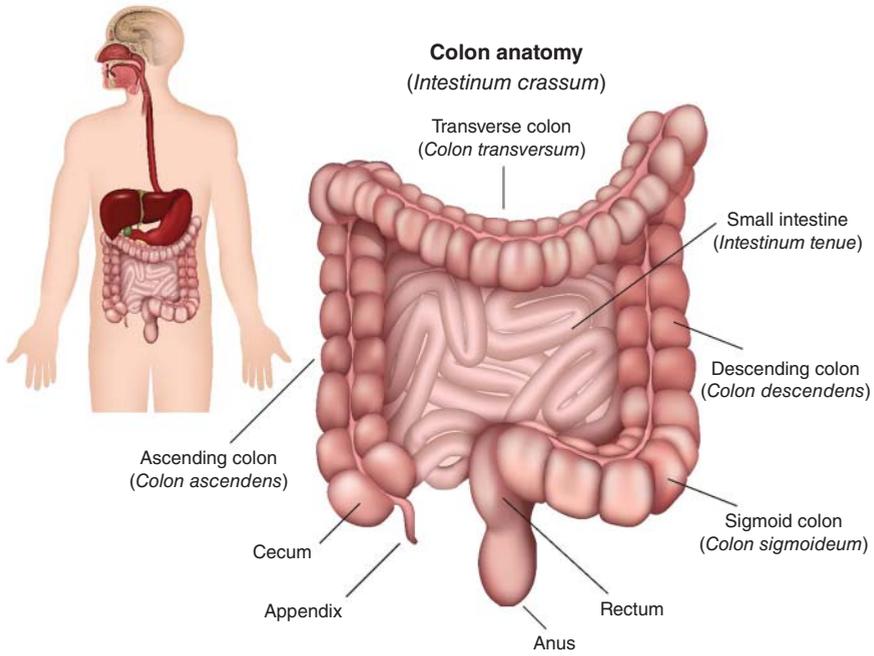


Figure 7.1 Anatomy of human colon (large intestine).

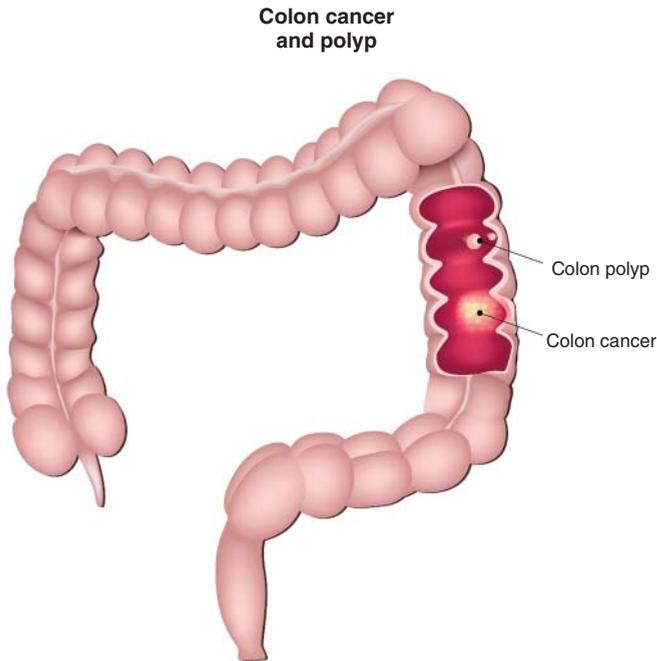


Figure 7.2 Cancer on colon.

- Weight loss
- Irritable bowel syndrome (IBS)
- Iron deficiency anemia

If the cancer spreads to another part of the body, additional symptoms can show in the new area [21–30]. Spreading colorectal cancer often invades the liver.

7.4 Stages

Colorectal cancers are categorized according to stages, depending on how far the cancer has spread. Below is a common four-stage account, with a description of the status of the cancer at the beginning of each stage:

Stage 0: The cancer is in a very early stage and has not grown outside the inner layer of the colon. It is known as carcinoma in situ.

Stage 1: The cancer has grown into the next layer of tissue, but has not reached the lymph nodes or other organs.

Stage 2: The cancer has reached the outer layers of the colon, but has not yet spread beyond the colon.

Stage 3: The cancer has progressed through the outer layers of the colon and has reached one to three lymph nodes. It has not spread to distant sites.

Stage 4: The cancer has reached other tissues beyond the wall of the colon. As stage 4 progresses, the cancer reaches more distant parts of the body.

7.5 Diagnosis

Along with conducting a complete physical examination, including obtaining family history information, a physician will order either a colonoscopy or a barium enema X-ray to check for any signs of developing polyps in the colon. During a colonoscopy, a long, flexible tube with a camera on one end is inserted into the rectum to inspect the inside of the colon. In a barium enema X-ray, the patient drinks a chalky liquid containing barium, which enables a detailed image of the colon to show up on an X-ray (Figure 7.3).

7.6 Methods of Treatment

Treatment for colorectal cancer is determined according to the type and stage of the cancer, as well as the age, health status, and other characteristics of the patient. The goal is to remove the cancer and relieve any painful symptoms. There is no single treatment for any cancer, but the most common options for colon cancer are surgery, chemotherapy, and radiation therapy [6, 31–143].

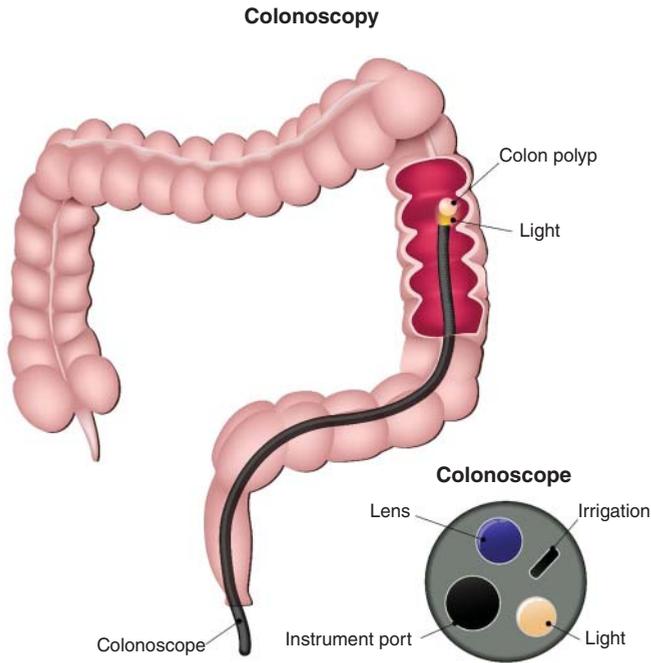


Figure 7.3 Check any colon polyp through colonoscope.

7.6.1 Surgery

In the early stage, cancer can be removed by surgical operation.

7.6.2 Radiation Therapy

The targeted radiation is used to kill cancer cells.

7.6.3 Chemotherapy

Common chemotherapy drugs for colon and rectal cancers are 5-fluorouracil (5-FU), capecitabine (Xeloda), irinotecan (Camptosar), leucovorin calcium and oxaliplatin (Eloxatin), trifluridine and tipiracil (Lonsurf), and others.

7.6.4 Targeted Therapy

Common targeted therapy drugs for colorectal cancers are bevacizumab (Avastin), ramucirumab (Cyramza), ziv-aflibercept (Zaltrap), cetuximab (Erbix), panitumumab (Vectibix), encorafenib (Braftovi), and regorafenib (Stivarga).

7.6.5 Immunotherapy

PD-1 inhibitors pembrolizumab (Keytruda) and nivolumab (Opdivo) and CTLA-4 inhibitor ipilimumab (Yervoy) are used to treat colorectal cancer.

7.7 Drugs to Anal Cancer

Anal cancer occurs in the anus. Common chemotherapy drugs for anal cancer are carboplatin, cisplatin, docetaxel, oxaliplatin, paclitaxel, and leucovorin. These drugs are used in combinations of two or three. Nivolumab (Opdivo) and pembrolizumab (Keytruda) are checkpoint inhibitors used as immunotherapy.

7.8 Drugs to Prevent Anal Cancer

Gardasil (recombinant HPV quadrivalent vaccine)
 Gardasil 9 (recombinant HPV nonavalent vaccine)
 Recombinant human papillomavirus (HPV) nonavalent vaccine
 Recombinant human papillomavirus (HPV) quadrivalent vaccine

7.8.1 Treatment Regimens for Colorectal Cancer: Adjuvant/Advanced/Metastatic Disease

Single-Agent Regimens

Capecitabine

850–1250 mg orally twice daily on days 1–14
 Repeat cycle every three weeks [65, 66].

Cetuximab (*KRAS/NRAS/BRAF* wild-type gene)

400 mg/m² IV over two hours' first infusion, then 250 mg/m² IV over 60 minutes weekly
 or 500 mg/m² IV over two hours on day 1
 Repeat cycle every two weeks [67].

5-Fluorouracil

2600 mg/m² IV over 24 hours' infusion on day 1 plus Leucovorin 500 mg/m²
 Repeat cycle every week [99].
 or 500 mg/m² IV infusion over two hours once a week
 Leucovorin: 500 mg/m² IV over two hours once a week
 Repeat cycle every week [136].

Irinotecan

125 mg/m² IV on days 1 and 8
 or 350 mg/m² or 300 mg/m² in patients >70 years of age on day 1
 Repeat cycle every three weeks [68].

Larotrectinib (*NTRK* gene fusion-positive)

100 mg orally twice daily.
 Continue until disease progression or unacceptable toxicity [69].

Entrectinib (*NTRK* gene fusion-positive)

600 mg orally once daily
 Continue until disease progression or unacceptable toxicity [131].

Nivolumab

3 mg/kg IV over 30 minutes on day 1, every two weeks
 or 240 mg IV every two weeks
 or 480 mg IV every four weeks [100].

Pembrolizumab

10 mg/kg IV over 30 minutes on day 1
 Repeat cycle every two weeks [101].

Panitumumab

6 mg/kg IV over 60 minutes on day 1
 Repeat cycle every two weeks until disease progression or unacceptable toxicity develops [70].

Regorafenib

160 mg orally once daily on days 1–21
 Repeat cycle every 28 days [102, 103].

Fam-trastuzumab deruxtecan-nxki

6.4 mg/kg IV on day 1
 Repeat every 21 days [132]

Dostarlimab-gxly

500 mg IV every three weeks for four doses followed by 1000 mg IV every six weeks until disease progression or unacceptable toxicity occurs [133].

7.8.2 Systemic Therapy for Advanced or Metastatic Disease**Combination Regimens****Leucovorin + 5-Fluorouracil (weekly schedule low dose)**

Leucovorin: 20 mg/m² IV over two hours on day 1, give first
 5-Fluorouracil: 500 mg/m² IV over one hour on day 1, give second
 Repeat cycle every week [104].

Leucovorin + 5-Fluorouracil (weekly schedule high dose)

Leucovorin: 500 mg/m² IV over two hours once every week
 5-Fluorouracil: 500 mg/m² IV over one hour once every week
 Repeat cycle every eight weeks [71, 72].

Capecitabine + Oxaliplatin (XELOX)

Capecitabine: 1000 mg/m² orally twice daily on days 1–14
 Oxaliplatin: 130 mg/m² IV over two hours on day 1
 Repeat cycle every three weeks for eight cycles [137].

Cetuximab + Bevacizumab

Cetuximab: 400 mg/m² IV over two hours' loading dose, followed by
250 mg/m² IV over 60 minutes weekly
Bevacizumab: 5 mg/kg IV over 90 minutes on day 1
Repeat cycle every two weeks [138].

Capecitabine + Mitomycin-C

Capecitabine: 1000 mg/m² orally twice daily on days 1–14, followed by
1-week rest, then on days 22–35, followed by 1-week rest
Mitomycin-C: 7 mg/m² IV on day 1
Repeat cycles every six weeks [108].

Encorafenib + Cetuximab (BRAF V600E mutation positive)

Encorafenib: 300 mg orally once daily on days 1–28
Cetuximab: 400 mg/m² IV over two hours first dose, then 250 mg/m²
IV over 60 minutes weekly
Repeat cycle every four weeks [139].

Nivolumab + Ipilimumab

Nivolumab: 3 mg/kg IV over 30 minutes on day 1
Ipilimumab: 1 mg/kg IV over 30 minutes on day 1
Repeat cycle every three weeks for four cycles and then use nivolumab 240 mg IV
over 30 minutes every two weeks [73].

Trifluridine + Tipiracil (TAS-102, Lonsurf)

35 mg/m² orally twice daily on days 1–5 and 8–12
Repeat cycle every four weeks [110].

Irinotecan + Bevacizumab

Irinotecan: 180 mg/m² IV over 30 minutes on day 1
Bevacizumab: 5 mg/kg IV on day 1
Repeat cycle every two weeks [111].

Irinotecan + Cetuximab

Cetuximab: 400 mg/m² IV over two hours' first dose, then 250 mg/m² IV
over 60 minutes weekly
Irinotecan: 350 mg/m² IV on day 1
Repeat cycle every three weeks [56].

Irinotecan + Panitumumab

Irinotecan: 180 mg/m² IV over 30 minutes on day 1, given second
Panitumumab: 6 mg/kg IV over 60 minutes on day 1, given first
Repeat cycle every two weeks [74].

FOLFOX

FOL = Folinic acid (leucovorin)

F = 5-Fluorouracil

OX = Oxaliplatin

Oxaliplatin + 5-Fluorouracil + Leucovorin (FOLFOX4)

Oxaliplatin: 85 mg/m² IV over two hours on day 1
 Leucovorin: 200 mg/m² IV over two hours on days 1 and 2
 5-Fluorouracil: 400 mg/m² IV bolus, followed by 600 mg/m² IV
 continuous 22 hours' infusion on days 1 and 2
 Repeat cycle every two weeks [49, 112].

Oxaliplatin + 5-Fluorouracil + Leucovorin (FOLFOX6)

Oxaliplatin: 85 mg/m² IV over three hours on day 1
 Leucovorin: 400 mg/m² IV over two hours' infusion on day 1
 5-Fluorouracil: 400 mg/m² IV bolus on day 1, followed by 1200 mg/m² IV
 continuous infusion over 22 hours
 Repeat cycle every two weeks for 8–12 cycles [76].

Oxaliplatin + 5-Fluorouracil + Leucovorin (m-FOLFOX6)

Oxaliplatin: 85 mg/m² IV over three hours on day 1
 Leucovorin: 400 mg/m² IV over two hours on day 1, oxaliplatin and
 leucovorin inject simultaneously with a Y-infusion device
 5-Fluorouracil: 400 mg/m² IV bolus on day 1, followed by 2400 mg/m² IV
 continuous infusion over 46–48 hours
 Repeat cycle every two weeks for 8–12 cycles [112].

Oxaliplatin + 5-Fluorouracil + Leucovorin (FOLFOX7)

Oxaliplatin: 85 mg/m² IV over two hours on day 1
 Leucovorin: 400 mg/m² IV over two hours on day 1
 5-Fluorouracil: 2400 mg/m² IV continuous infusion on days 1 and 2
 over 46–48 hours
 Repeat cycle every two weeks [77].

mFOLFOX6 + Bevacizumab

Bevacizumab: 5 mg/kg IV over 90 minutes on day 1, given first
 Oxaliplatin: 85 mg/m² IV over two hours on day 1
 Leucovorin: 400 mg/m² IV over two hours on day 1
 5-Fluorouracil: 400 mg/m² IV bolus on day 1, then 2400 mg/m² IV
 continuous infusion on days 1 and 2 over 46–48 hours
 Repeat cycle every two weeks [79, 80, 135].

mFOLFOX6 + Cetuximab

Cetuximab: 400 mg/m² IV over two hours on day 1, followed by 250 mg/m² IV over 60 minutes weekly, given first each cycle

Oxaliplatin: 85 mg/m² IV over two hours on day 1

Leucovorin: 400 mg/m² IV over two hours on day 1

5-Fluorouracil: 400 mg/m² IV bolus on day 1, then 2400 mg/m² IV continuous infusion on days 1 and 2 over 46–48 hours

Repeat cycle every two weeks [80].

FOLFOX4 + Panitumumab

Panitumumab: 6 mg/kg IV one hour infusion on day 1

Oxaliplatin: 85 mg/m² IV over two hours on day 1

Leucovorin: 400 mg/m² IV over two hours on day 1

5-Fluorouracil: 400 mg/m² IV bolus on day 1, then 600 mg/m² IV over 22 hours' continuous infusion on days 1 and 2

Repeat cycle every two weeks [115].

Trastuzumab + Lapatinib (HER2-positive *KRAS* codon 12/13 wild-type)

Trastuzumab: 4 mg/kg IV loading dose on day 1 of cycle 1, followed by 2 mg/kg IV once per week

Lapatinib: 1000 mg orally once daily on days 1–7

Repeat cycle every week until evidence of disease progression [78].

Trastuzumab + Pertuzumab (HER2-positive, mutations in *KRAS*, *BRAF* wild-type, *PIK3CA*)

Trastuzumab: 8 mg/kg IV loading dose on day 1 of cycle 1, followed by 6 mg/kg IV every 21 days

Pertuzumab: 840 mg IV loading dose on day 1 of cycle 1, followed by 420 mg IV every 21 days

Repeat cycle every 21 days [114].

Capecitabine + Oxaliplatin + Bevacizumab

Bevacizumab: 7.5 mg/kg IV 30–90 minutes' infusion on day 1

Capecitabine: 850 mg/m² orally twice daily on days 1–14

Oxaliplatin: 130 mg/m² IV over two hours on day 1

Repeat cycle every three weeks [106, 117].

5-Fluorouracil + Leucovorin + Bevacizumab

Bevacizumab: 5 mg/kg IV over 60 minutes every two weeks

Leucovorin: 500 mg/m² IV over two hours weekly for six weeks

5-Fluorouracil: 500 mg/m² IV weekly for six weeks

Repeat cycle every eight weeks [118].

FOLFOXIRI

FOL = Folinic acid (Leucovorin)

F = 5-Fluorouracil

OX = Oxaliplatin

IRI = Irinotecan

FOLFOXIRI

- Irinotecan: 165 mg/m² IV infusion over 30–90 minutes on day 1
 Oxaliplatin: 85 mg/m² IV infusion over two hours on day 1
 Leucovorin: 400 mg/m² IV infusion over two hours on day 1, concurrently with oxaliplatin through a Y-connector
 5-Fluorouracil: 3200 mg/m² IV continuous infusion for 46 hours on days 1 and 2 for European patients (for US patients, dose of 5-Fluorouracil is 2400 mg/m² IV continuous infusion over 46–48 hours for all FOLFOXIRI regimens)

Repeat cycle every two weeks until evidence of progression, unacceptable toxicity, patient refusal, or for a total of 12 cycles [81].

FOLFOXIRI + Bevacizumab

- Bevacizumab: 5 mg/kg IV infusion over 30 minutes on day 1
 Irinotecan: 165 mg/m² IV over 60 minutes on day 1
 Oxaliplatin: 85 mg/m² IV over two hours on day 1
 Leucovorin: 200 mg/m² IV over two hours on day 1, concurrently with oxaliplatin through a Y-connector
 5-Fluorouracil: 2400 mg/m² IV continuous infusion over 46 hours on days 1 and 2

Repeat cycle every two weeks [82, 119].

FOLFOXIRI + Cetuximab (mutation of genes in *KRAS/NRAS/BRAF* wild-type)

- Cetuximab: 500 mg/m² IV over 60 minutes on day 1 for week 1, then 250 mg/m² IV over 30 minutes starting week 2
 Irinotecan: 130 mg/m² IV over 60 minutes on day 1
 Oxaliplatin: 85 mg/m² IV over two hours on day 1
 Leucovorin: 200 mg/m² IV over two hours on day 1, concurrently with oxaliplatin through a Y-connector
 5-Fluorouracil: 2400 mg/m² IV continuous infusion for 46 hours on days 1 and 2

Repeat cycle every two weeks [120].

FOLFOXIRI + Panitumumab (*KRAS* codon 61, *HRAS*, *NRAS*, and *BRAF* V600E mutations)

- Panitumumab: 6 mg/kg IV over 60 minutes on day 1
 Irinotecan: 150 mg/m² IV over 60 minutes on day 1
 Oxaliplatin: 85 mg/m² IV over two hours on day 1
 Leucovorin: 200 mg/m² IV over two hours on day 1, concurrently with oxaliplatin through a Y-connector
 5-Fluorouracil: 2400 mg/m² IV continuous infusion over 46 hours on days 1 and 2

Repeat cycle every two weeks [121].

Irinotecan + 5-Fluorouracil + Leucovorin (FOLFIRI)

FOL = Folinic acid (Leucovorin)

F = 5-Fluorouracil

IRI = Irinotecan

Irinotecan: 180 mg/m² IV over two hours on day 1

Leucovorin: 400 mg/m² IV over two hours on day 1, concurrently with irinotecan through a Y-connector

5-Fluorouracil: 400 mg/m² IV bolus on day 1, followed by 2400 mg/m² IV continuous infusion over 46–48 hours on days 1 and 2

Repeat cycle every two weeks [122].

Irinotecan + 5-Fluorouracil + Leucovorin + Bevacizumab (FOLFIRI + Bevacizumab)

Bevacizumab: 5 mg/kg IV on day 1

Irinotecan: 180 mg/m² IV over two hours on day 1

Leucovorin: 400 mg/m² IV over two hours on day 1, concurrently with irinotecan through a Y-connector

5-Fluorouracil: 400 mg/m² IV bolus on day 1, followed by 2400 mg/m² IV continuous infusion over 46–48 hours on days 1 and 2

Repeat cycle every two weeks [83].

Irinotecan + 5-Fluorouracil + Leucovorin + Cetuximab (FOLFIRI + Cetuximab) (mutation of genes in *KRAS/NRAS/BRAF* wild-type)

Cetuximab: 400 mg/m² IV over two hours loading dose, then 250 mg/m² IV over 60 minutes weekly

Irinotecan: 180 mg/m² IV over 30–90 minutes on day 1

Leucovorin: 400 mg/m² IV over two hours on day 1, concurrently with irinotecan through a Y-connector

5-Fluorouracil: 400 mg/m² IV bolus on day 1, followed by 2400 mg/m² IV continuous infusion over 46–48 hours on days 1 and 2

Repeat cycle every two weeks [56, 83].

Irinotecan + 5-Fluorouracil + Leucovorin + Panitumumab (FOLFIRI + Panitumumab) (*KRAS/NRAS/BRAF* wild-type only)

Panitumumab: 6 mg/kg IV over 60 minutes on day 1

Irinotecan: 180 mg/m² IV over two hours on day 1

Leucovorin: 400 mg/m² IV over two hours on day 1, concurrently with irinotecan through a Y-connector

5-Fluorouracil: 400 mg/m² IV bolus on day 1, followed by 2400 mg/m² IV continuous infusion over 46–48 hours on days 1 and 2

Repeat cycle every two weeks [84].

Irinotecan + 5-Fluorouracil + Leucovorin + Ziv-aflibercept (FOLFIRI + Ziv-aflibercept)

Ziv-aflibercept: 4 mg/kg IV over 60 minutes on day 1
 Irinotecan: 180 mg/m² IV over two hours on day 1
 Leucovorin: 400 mg/m² IV over two hours on day 1, concurrently with irinotecan through a Y-connector
 5-Fluorouracil: 400 mg/m² IV bolus on day 1, followed by 2400 mg/m² IV continuous infusion over 46–48 hours on days 1 and 2
 Repeat cycle every two weeks [75].

Irinotecan + 5-Fluorouracil + Leucovorin + Ramucirumab (FOLFIRI + Ramucirumab)

Ramucirumab: 8 mg/kg IV over 60 minutes on day 1
 Irinotecan: 180 mg/m² IV over 30–90 minutes on day 1
 Leucovorin: 400 mg/m² IV over two hours on day 1, concurrently with irinotecan through a Y-connector
 5-Fluorouracil: 400 mg/m² IV bolus on day 1, followed by 2400 mg/m² IV continuous infusion over 46–48 hours on days 1 and 2
 Repeat cycle every two weeks [51].

Cetuximab + Irinotecan + Vemurafenib

Cetuximab: 500 mg/m² IV over 60 minutes on day 1
 Irinotecan: 180 mg/m² IV over 30–90 minutes on day 1
 Vemurafenib: 960 mg orally twice daily on days 1–14
 Repeat cycle every two weeks [85].

Irinotecan + Panitumumab + Vemurafenib

Panitumumab: 6 mg/kg IV over 60 minutes on day 1
 Irinotecan: 180 mg/m² IV over 60–90 minutes on day 1
 Vemurafenib: 960 mg orally twice daily on days 1–14
 Repeat cycle every two weeks [85].

Irinotecan + Capecitabine + Bevacizumab (XELIRI + Bevacizumab)

Bevacizumab: 7.5 mg/kg IV over 60 minutes on day 1
 Irinotecan: 200 mg/m² IV over 30–90 minutes on day 1
 Capecitabine: 800 mg/m² orally once daily on days 1–14
 Repeat cycle every three weeks [124].

Binimetinib + Encorafenib + Cetuximab

Binimetinib: 45 mg orally twice daily on days 1–28
 Encorafenib: 300 mg orally once daily on days 1–28
 Cetuximab: 400 mg/m² IV over two hours on day 1 for week 1, then 250 mg/m² IV over 60 minutes starting week 2
 Repeat cycle every four weeks [86].

7.8.3 Treatment Regimens for Anal Cancer: Regimens for Localized Stage

5-Fluorouracil + Mitomycin-C + Radiation Therapy

5-Fluorouracil: 1000 mg/m² IV daily continuous infusion over 24 hours on days 1–4 and 29–32
 Mitomycin-C: 10 mg/m² IV (maximum 20 mg) on days 1 and 29
 Radiation: 45–59 Gy/day
 Chemotherapy is given at the same time with radiation [87, 140, 141].

Capecitabine + Mitomycin-C + Radiation Therapy

Capecitabine: 825 mg/m² orally twice daily from Monday–Friday
 Mitomycin-C: 10 mg/m² IV (maximum 20 mg) on days 1 and 29
 Radiation: 25–63 Gy
 Chemotherapy is given concurrently with radiation [88, 89, 140].

5-Fluorouracil + Cisplatin + Radiation Therapy

5-Fluorouracil: 1000 mg/m² IV daily continuous infusion over 24 hours on days 1–4 of each week of radiation
 Cisplatin: 75 mg/m² IV over 60 minutes on days 1, 29, 57, and 85 during radiation therapy
 Radiation: Total dose, 4500 cGy over five weeks
 Chemotherapy is given concurrently with radiation [90, 91].

Capecitabine + Oxaliplatin + Radiation therapy

Capecitabine: 825 mg/m² orally twice daily from Monday–Friday for six weeks
 Oxaliplatin: 50 mg/m² IV on days 1, 8, 22, and 29
 Radiation: 180 cGy/day, five days/week for a maximum of six weeks
 Chemotherapy is given concurrently with radiation [92].

7.8.4 Treatment Regimens for Anal Cancer: Metastatic Stage

5-Fluorouracil + Cisplatin

5-Fluorouracil: 1000 mg/m²/day IV continuous infusion over 24 hours on days 1–5
 Cisplatin: 60–100 mg/m² IV over 60 minutes on day 1
 Repeat cycle every 28 days [93].

Carboplatin + Paclitaxel

Carboplatin: AUC of 5, IV infusion over 30 minutes on day 1
 Paclitaxel: 175 mg/m² IV infusion over three hours on day 1
 Repeat cycle every three weeks [94].

mFOLFOX6

Oxaliplatin: 85 mg/m² IV over two hours on day 1
 Leucovorin: 400 mg/m² IV over two hours on day 1
 5-Fluorouracil: 400 mg/m² IV bolus on day 1, then 2400 mg/m² IV continuous infusion over 46 hours (1200 mg/m² /day × 2 days total 2400 mg/m²)
 Repeat cycle every two weeks [95].

FOLCIS (5-Fluorouracil Continuous Infusion/Leucovorin/Cisplatin)

Cisplatin: 40 mg/m² IV over 30 minutes on day 1
 Leucovorin: 400 mg/m² IV over 30 minutes on day 1
 5-Fluorouracil: 400 mg/m² IV bolus on day 1, then 2000 mg/m² IV continuous infusion over 46 hours
 Repeat cycle every two weeks [96].

DCF

Docetaxel: 40 mg/m² IV on day 1
 Cisplatin: 40 mg/m² IV on day 1
 5-Fluorouracil: 1200 mg/m²/day × 2 days IV continuous infusion (total 2400 mg/m² over 46–48 hours)
 Repeat cycle every two weeks [130].

Nivolumab

240 mg IV over 30 minutes on day 1
 Repeat cycle every two weeks.
 or
 480 mg IV over 60 minutes on day 1
 Repeat cycle every four weeks.
 or
 3 mg/kg IV over 30 minutes on day 1
 Repeat cycle every two weeks for up to two years or until disease progression, unacceptable toxicity, or patient/investigator decision [97].

Pembrolizumab

200 mg/kg IV over 30 minutes on day 1
 Repeat cycle every three weeks.
 or
 10 mg/kg IV over 30 minutes on day 1
 Repeat cycle every two weeks for up to two years or until disease progression, unacceptable toxicity, or patient/investigator decision [64, 98].

7.9 Risk Factors/Possible Preventions

In addition to obtaining recommended periodic colonoscopy or barium enema X-ray screenings, individuals are advised as follows:

- Maintain a healthy weight
- Exercise
- Eat plenty of fruits, vegetables, and whole grains
- Avoid eating saturated fat and red meat
- Eliminate or minimize alcohol consumption
- Avoid smoking and secondhand smoke

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8

Cervical Cancer

8.1 Introduction

The cervix is at the lowest portion of a female's uterus and is a passageway connecting the uterus with the vagina. Cervical cancer can develop in the cells lining the cervix (Figure 8.1), resulting in abnormal growth of cancerous cells [1–61]. When invasive, the cancer spreads to deeper tissues of the cervix and possibly to other organs if it metastasizes. Most commonly affected by metastasized cervical cancer are the lungs, liver, bladder, vagina, and rectum.

8.2 Causes of Cervical Cancer

Infection with human papillomavirus (HPV) is the main cause of cervical cancer, and HPV can be transmitted sexually [1–8]. There are many subtypes of HPV, and they all do not cause cervical cancer. It should be noted that HPV is a different virus entirely from HIV.

8.3 Symptoms of Cervical Cancer

- Abnormal vaginal bleeding, such as after intercourse, between menstrual periods, or after menopause; menstrual periods may be heavier and last longer than normal
- Pain during intercourse
- Increased vaginal discharge and odor
- Unexplained, persistent pelvic and/or back pain
- If cervical cancer has spread to nearby tissues, symptoms may include:
 - Difficulty urinating, pain when urination, or blood in the urine
 - Dull backache or swelling in the legs
 - Diarrhea or pain or bleeding from the rectum after a bowel movement
 - Fatigue and loss of appetite
 - General feeling of illness
 - Weight loss
 - Swollen abdomen, nausea, vomiting, and constipation

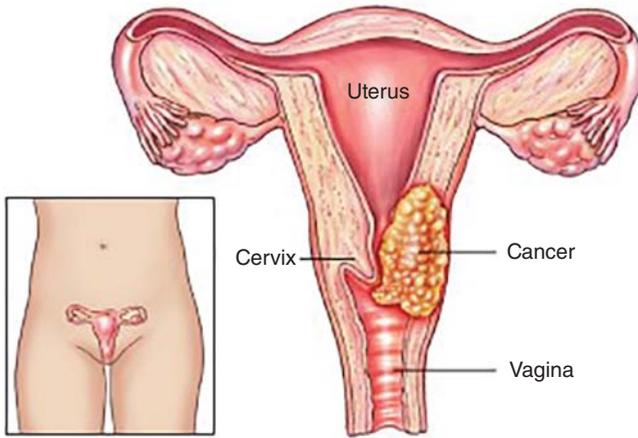


Figure 8.1 Cervical cancer.

8.4 Diagnosis

The presence of cervical cancer can be detected through routine **Pap screening** (or Pap smear). In conjunction with the Pap screening, females can be tested for HPV, another indicator of possible cervical cancer [14–21]. If a female’s Pap screening results are abnormal, the physician may order a **colposcopy**, which is a procedure using an instrument called a colposcope to examine cells in the genital area more closely. A colposcopy can be used to diagnose cervical cancer, genital warts, vaginal cancer, and vulvar cancer.

Physicians can also determine if a patient’s cervix feels or appears abnormal during a pelvic exam, and all women should report any unexplained bleeding or symptoms

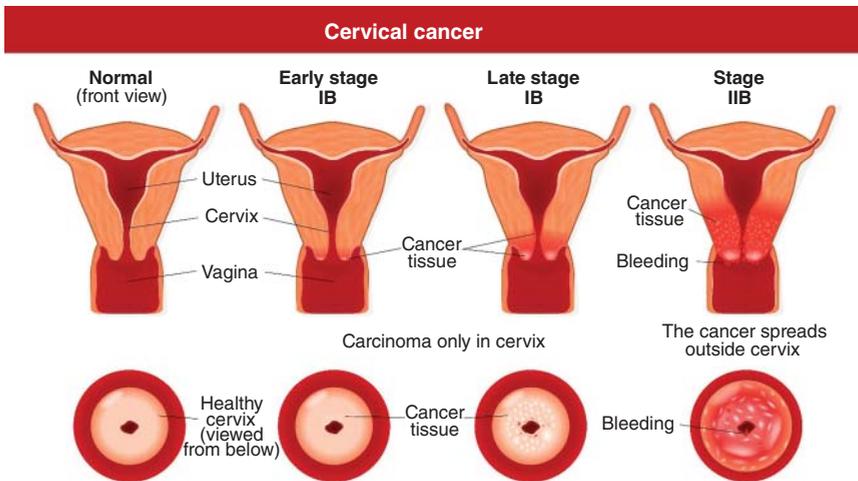


Figure 8.2 Stages of cervical cancer.

in the pelvic region. Like other types of cancer, cervical cancer is classified in terms of stages, with the progression and seriousness of the condition increasing accordingly (Figure 8.2).

8.5 Methods of Treatment

Cervical cancer is very treatable, especially if detected early [22–93]. There are several treatment options, including the following:

8.5.1 Surgery

Surgery is used to remove a tumor from the cervix.

8.5.2 Radiation Therapy

High-energy X-rays or other radioactive particle sources are used to destroy the cancer.

8.5.3 Chemotherapy

Common chemotherapy drugs for cervical cancer are cisplatin, carboplatin, docetaxel, ifosfamide, irinotecan, paclitaxel, gemcitabine, bleomycin, topotecan, 5-fluorouracil, and mitomycin.

8.5.4 Targeted Therapy

Avastin is a type of monoclonal antibody (an antibody produced in a lab for fighting specific cellular invaders) that can be used for the targeted treatment of cervical cancer. The drug specifically acts on cellular vascular endothelial growth factor, which is released by tumor cells and aids in their proliferation.

8.5.5 Immunotherapy

Immune checkpoint inhibitor pembrolizumab (Keytruda) targets PD-1 and is used for cervical cancer treatment.

8.6 Vaccines to Prevent Cervical Cancer

There are several vaccines to prevent cervical cancer:

- Cervarix (recombinant HPV bivalent vaccine)
- Gardasil (recombinant HPV quadrivalent vaccine)
- Gardasil 9 (recombinant HPV nonavalent vaccine)
- Recombinant human papillomavirus (HPV) bivalent vaccine
- Recombinant human papillomavirus (HPV) nonavalent vaccine
- Recombinant human papillomavirus (HPV) quadrivalent vaccine

8.7 Treatment Regimens: Systemic Therapy for Recurrent or Metastatic Cervical Cancer

Single-Agent Regimens

Bevacizumab

15 mg/kg IV on day 1

Repeat cycle every three weeks [58].

Cisplatin

50 mg/m² IV on day 1

Repeat cycle every 21 days for six cycles [66].

Carboplatin

400 mg/m² on day 1

Repeat cycle every four weeks [67, 68].

Docetaxel

100 mg/m² IV on day 1

Repeat cycle every three weeks [60].

Gemcitabine

800 mg/m² IV on days 1, 8, and 15

Repeat cycle every four weeks [69, 70].

Irinotecan

125 mg/m² IV weekly for four weeks

Repeat cycle every six weeks (four weeks on followed by two weeks off) [71].

Paclitaxel

175 mg/m² IV over three hours on day 1

Repeat cycle every three weeks

or

80 mg/m² IV over 60 minutes

Repeat cycle weekly [73, 91].

Albumin-bound Paclitaxel

125 mg/m² IV over 30 minutes on days 1, 8, and 15

Repeat cycle every 28 days [74, 75].

Pembrolizumab

200 mg IV on day 1

Repeat cycle every 21 days for two years or until progression, intolerable toxicity, or physician or patient decision [76].

Pemetrexed

500 mg/m² IV on day 1, repeat cycle every 21 days or 900 mg/m² IV every three weeks. Initiate folic acid 400–1000 µg orally once daily, beginning seven days before the first dose of pemetrexed. Administer vitamin B12, 1 mg intramus-

cularly, one week prior to the first dose of pemetrexed and every three cycles thereafter [77, 78].

Do not substitute oral vitamin B12 for intramuscular vitamin B12.

Topotecan

1.5 mg/m² IV on days 1–5

Repeat cycle every three weeks

or

3 mg/m² IV on days 1, 8, and 15

Repeat cycle every 28 days [79, 80].

Vinorelbine

30 mg/m² IV on days 1 and 8

Repeat cycle every 21 days [81].

Cisplatin + Radiation Therapy

Cisplatin: 40 mg/m² IV weekly

Radiation: 1.8–2 Gy per fraction

Cisplatin is given four hours before radiation. Repeat cycle weekly for six weeks with concurrent radiation [82].

Combination Regimens

Cisplatin + 5-Fluorouracil

Cisplatin: 50–75 mg/m² IV infusion at a rate of 1 mg/min on day 1

5-Fluorouracil: 1000 mg/m²/day IV infusion over 24 hours daily on days 2–5

Repeat cycle every three weeks [83].

Cisplatin + Irinotecan

Cisplatin: 60 mg/m² IV over 90 minutes on day 1, given second

Irinotecan: 60 mg/m² IV over 90 minutes on days 1, 8, and 15, given first

Repeat cycle every 28 days for a maximum of six cycles [84].

Cisplatin + Paclitaxel

Paclitaxel: 135 mg/m² IV continuous infusion over 24 hours on day 1

Cisplatin: 50 mg/m² IV over 60 minutes on day 2

Repeat cycle every three weeks for six cycles [66].

Cisplatin + Topotecan

Cisplatin: 50 mg/m² IV over 60 minutes on day 1, given second

Topotecan: 0.75 mg/m²/day IV daily on days day 1–3, given first

Repeat cycle every three weeks [85].

Cisplatin + Pemetrexed

Pemetrexed: 500 mg/m² IV infusion over 10 minutes on day 1
 Cisplatin: 50 mg/m² IV over 60 minutes on day 1
 Initiate folic acid 350–1000 µg orally once daily, beginning seven days before the first dose of pemetrexed. Administer vitamin B12, 1 mg intramuscularly, one week prior to the first dose of pemetrexed and every three cycles thereafter. Repeat cycle every 21 days until disease progression or adverse events prohibited further therapy [86].
 Do not substitute oral vitamin B12 for intramuscular vitamin B12.

Cisplatin + Vinorelbine

Vinorelbine: 25 mg/m² IV on days 1 and 8
 Cisplatin: 80 mg/m² IV over 80 minutes on day 1
 Repeat cycle every three weeks [87].

Carboplatin + Docetaxel

Docetaxel: 60 mg/m² IV on day 1
 Carboplatin: AUC of 6, IV over 30 minutes on day 1
 Repeat cycle every three weeks [88].

Paclitaxel + Topotecan

Paclitaxel: 175 mg/m² IV infusion over three hours on day 1
 Topotecan: 0.75 mg/m² IV over 30 minutes on days 1–3
 Repeat cycle every 21 days and continue until disease progression or the development of unacceptable toxic effects [56].

5-Fluorouracil + Leucovorin

Leucovorin: 200 mg/m² IV bolus daily on days 1–5
 5-Fluorouracil: 370 mg/m² IV bolus daily on days 1–5
 Repeat cycle every four weeks [89].

Cisplatin + Paclitaxel + Bevacizumab

Paclitaxel: 175 mg/m² IV over three hours on day 1
 Cisplatin: 50 mg/m² IV over 60 minutes on day 1
 Bevacizumab: 15 mg/kg IV on day 1
 Repeat cycle every three weeks [56].

Paclitaxel + Topotecan + Bevacizumab

Paclitaxel: 175 mg/m² IV over three hours on day 1
 Topotecan: 0.75 mg/m² IV over 30 minutes on days 1–3
 Bevacizumab: 15 mg/kg IV on day 1
 Repeat cycle every 21 days [56].

Carboplatin + Paclitaxel + Bevacizumab

Paclitaxel: 175 mg/m² IV over three hours on day 1
 Carboplatin: AUC of 5, IV over 30 minutes on day 1
 Bevacizumab: 15 mg/kg IV on day 1
 Repeat cycle every 21 days [92, 93].

8.8 Risk Factors/Possible Preventions

Cervical cancer is highly preventable for most women due to the availability of routine screening tests (Pap screening) and a vaccine to guard against HPV infection, which is linked to the development of cervical cancer as mentioned above [22, 24, 34, 35, 37]. Women are advised to begin obtaining routine Pap testing at 21 years of age.

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9

Kidney Cancer

9.1 Introduction

The kidneys are a pair of organs located in the abdominal cavity, with each kidney being about the size of a person's fist. The part of the urinary tract, the kidneys help the body process waste as urine and filter blood before sending it back to the heart. The kidneys have many crucial functions:

- Maintaining overall fluid balance.
- Removing extra water from the blood.
- Regulating and filtering minerals from the blood.
- Filtering waste materials from food, medications, and toxic substances.
- Creating hormones that help produce red blood cells, promote bone health, and regulate blood pressure.

9.2 Genes Associated with Kidney Cancer

Cancer begins when there is a mutation of certain genes within the cells of this organ, resulting in an uncontrolled proliferation of cancer cells (Figure 9.1) that form a tumor inside the kidney [1–45]. The two most common types of kidney cancer are renal cell carcinoma (RCC) and transitional cell carcinoma (TCC), also known as urothelial cell carcinoma of the renal pelvis. These names are derived from the type of cell where cancer first appeared. Some inherited genes' mutations (changes) can find in some families and increase the risk of kidney cancer including *VHL 3p26* (tumor suppressor gene, caused to von Hippel-Lindau disease), *FH* genes (linked to hereditary leiomyomas and fibroids in the skin and uterus), *FLCN* gene (linked to Birt-Hogg-Dube syndrome), and *SDHB* and *SDHD* genes (for familial renal cancer) [1–15].

According to the National Cancer Institute, kidney cancer is the eighth most common cancer in the United States, with an estimated 65 340 new cases diagnosed in 2018.

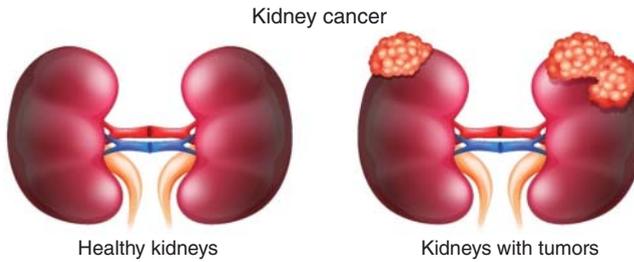


Figure 9.1 Kidney cancer.

9.3 Types of Kidney Cancer

Renal cell carcinoma (RCC) comprises approximately 85% of adult kidney cancer diagnoses, and the most common form of this type is called *clear cell RCC*. When the cells that form this type of cancer are viewed under a microscope, they appear pale and clear. The second most frequently encountered type of RCC is called *papillary RCC*. In this type, cancer forms small projections called papillae in some or most of the tumors.

Another 10–15% of kidney cancer is **urothelial cell carcinoma** of the renal pelvis. Other, rarer types of kidney cancer are **sarcomas**, **Wilms' tumor** (seen most commonly in children under five years of age), and **lymphomas**.

9.4 Kidney Cancer Symptoms

- Blood in the urine
- A lump in the abdomen or side
- Loss of appetite
- Persistent pain in the side
- Unexplained weight loss
- Fever that lasts for weeks, not caused by a cold or other infection
- Extreme fatigue
- Anemia
- Swelling in ankles or legs
- Kidney cancer that has spread to other parts of the body may cause additional symptoms, such as:
 - Shortness of breath
 - Coughing up blood
 - Pain in one or more bones

9.5 Diagnosis

There are several means by which physicians can detect or diagnose kidney cancer [13–15].

9.5.1 Urine Tests

Urine samples that contain blood can alert a physician to possible issues and the need for additional testing.

9.5.2 Blood Tests

Checking for levels of various chemical components and degree of filtration show how well the kidneys are functioning.

9.5.3 Biopsy

A biopsy consists of the removal of any suspicious tissue for further analysis and determination of whether cancer cells are present.

9.5.4 Intravenous Pyelogram

A medical specialist injects a dye into the body, which travels to the urinary tract. After the dye is in place, an X-ray screening is performed to detect tumors on the kidneys.

9.5.5 Ultrasound

This type of imaging test utilizes sound waves to create a picture of the kidneys. It can provide information as to whether a tumor is solid or fluid-filled.

9.5.6 Computed Tomography Scan

As described previously, this screening test combines X-rays with computer technology to create a series of very detailed pictures of the kidneys. Some computed tomography (CT) scans make use of a dye for needed contrast. CT scans have virtually replaced the intravenous pyelogram (IVP) and ultrasound in effectively diagnosing kidney cancer.

9.5.7 Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) may also involve the injection of a contrast agent to create better, more informative pictures.

9.5.8 Renal Arteriogram

This test makes use of X-ray screening along with a special type of contrast material injected into blood vessels, to give physicians information about the kidney tumor's blood supply.

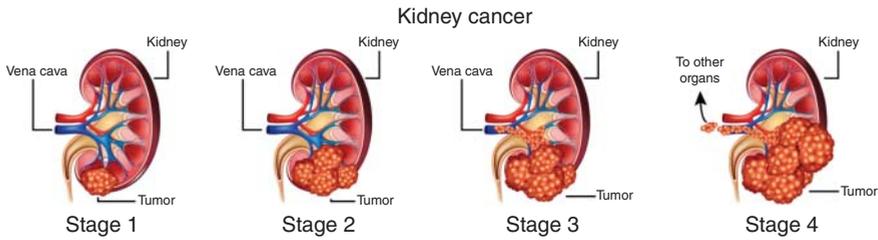


Figure 9.2 Stages of kidney cancer.

9.6 Kidney Cancer Stages

Like other types of cancer, kidney cancer is categorized in terms of stages, with the progression and seriousness of the condition increasing accordingly (Figure 9.2).

Stage I: A tumor 7 cm or smaller that is only in one kidney. The 5-year survival rate for stage I kidney cancer is approximately 81%, meaning that 81 people out of 100 will be alive five years after being diagnosed.

Stage II: A tumor larger than 7 cm that is only in one kidney.

Stage III: Two scenarios are described by this stage. The first is that the tumor has grown from the kidney into a major vein and nearby tissue, but has not yet reached nearby lymph nodes. The second is that the tumor is of any size and may appear outside the kidney. The cancer cells have also reached nearby lymph nodes, but have not progressed further.

Stage IV: Two more scenarios are described by this stage, in which only 8 out of 100 individuals survive five years post-diagnosis. In this stage, the tumor has grown in size and reached tissue beyond the kidney. It may or may not have spread to nearby lymph nodes, but still has not metastasized (spread to other organs via the lymphatic system). The second scenario in this stage is a tumor that has grown in size, maybe in the lymph nodes, and has metastasized to other organs or additional lymph nodes.

9.7 Methods of Treatment

Currently, several treatment options are available [16–67].

9.7.1 Simple Nephrectomy

A procedure in which the affected kidney is removed.

9.7.2 Partial Nephrectomy

The kidney with cancer is removed along with some tissue surrounding it. This procedure is used for patients with smaller tumors (less than 4 cm).

9.7.3 Radical Nephrectomy

In this procedure, the kidney is removed along with the adrenal gland (adjacent to the kidney) and the surrounding tissue. Also, nearby lymph nodes are frequently removed. This is the most common surgery for kidney cancer and can now be performed through a small incision and use of a *laparoscope*, a long, thin tube illuminated with optic fibers that can be used as a probing and diagnostic tool, as well as for minor surgical resections.

9.7.4 Radiofrequency Ablation

In this procedure, high-energy radio waves are directed at the tumor to destroy it.

9.7.5 Arterial Embolization

The material is placed into the artery leading to the kidney for the purpose of blocking blood flow to the tumor in order to kill the cells.

9.7.6 Cryotherapy

Extreme cold is used to kill the tumor.

9.7.7 Radiation Therapy

High-energy radiation is directed at the tumor in order to destroy cancer cells.

9.7.8 Chemotherapy

Chemotherapy is not a standard therapy as most cases of kidney cancer are resistant to chemotherapy. Cisplatin, 5-fluorouracil (5-FU), capecitabine (Xeloda), and gemcitabine are used with a small number of patients.

9.7.9 Targeted Drug Therapy

A variety of medicines designed to kill kidney cancer cells are used most frequently in advanced stages of the disease in order to slow the spread of cancer for as long as possible. These very specialized formulations interfere with cellular mechanisms stimulating the growth of cancer cells. Examples of targeted therapy drugs are sunitinib (Sutent[®]), sorafenib, (Nexavar[®]), bevacizumab (Avastin[®]), temsirolimus (Torisel[®]), pazopanib (Votrient), cabozantinib (Cabometyx), lenvatinib (Lenvima), axitinib (Inlyta), tivozanib (Fotivda), and everolimus (Afinitor).

9.7.10 Immunotherapy

As discussed earlier, this mode of treatment involves administering drugs designed to boost a patient's own immune system to attack cancer cells and kill them. Immunotherapy and targeted drug therapy (discussed later) are used instead of chemotherapy for kidney cancer because cancer in this organ has been found

unresponsive to regular chemotherapy agents. Examples of immunotherapy drugs include pembrolizumab (Keytruda) and nivolumab (Opdivo) as PD-1 inhibitors; avelumab (Bavencio) as a PD-L1 inhibitor; ipilimumab (Yervoy) as a CTLA-4 inhibitor; and interleukin-2 (IL-2) and interferon-alfa as cytokine proteins.

9.7.11 Complementary or Alternative Treatment

Sometimes opted for alongside, or instead of, mainstream medical treatment, these types of therapies include such things as taking specific vitamins or herbal remedies, massage, music, homeopathic formulations, etc. The use of these treatments is the choice of the patient. It should be considered, however, that although some claim to cure cancer, none has been clinically proven to do so.

9.7.12 Drugs for Upper Tract Urothelial Cancer

Mitomycin is used for this type of cancer.

9.7.13 Drugs for Wilms' Tumor and Other Childhood Kidney Cancers

Dactinomycin, doxorubicin hydrochloride, and vincristine sulfate are used to treat this type of cancer.

9.8 Treatment Regimens

Renal cell carcinoma treatment regimens

Metastatic/ Relapse or Stage IV Therapy

Single-agent Regimens

Axitinib

5–10 mg orally twice daily
Repeat cycle every four weeks [52–54].

Cabozantinib

60 mg orally once daily on days 1–28
Repeat cycle every six weeks (4 weeks on/2 weeks off) [39, 55].

Everolimus

10 mg orally once daily
Continue until disease progression or intolerable toxicity [56].

Nivolumab

240 mg IV on day 1
Repeat cycle every two weeks [32, 33].

Aldesleukin (IL-2)

600 000 IU/kg IV every eight hours on days 1–5 and 15–19
Repeat cycle every 12 weeks for a total of three cycles [17].

Interferon α -2a

5–15 million international unit subcutaneously (SC) daily or 3–5 times per week
Continue until disease progression or unacceptable toxicity [17, 66].

Temsirolimus

25 mg IV on day 1
Repeat cycle every week and continue until disease progression or unacceptable toxicity [16].

Pazopanib

800 mg orally once daily
Continue until disease progression or unacceptable toxicity [57].

Sorafenib

400 mg orally twice daily
Continue until disease progression or unacceptable toxicity [40].

Sunitinib

50 mg orally once daily on days 1–28
Repeat cycle every six weeks (28 days on and 14 days off [30, 37].

Bevacizumab

10 mg/kg IV on day 1
Repeat cycle every two weeks [58].

Combination Regimens**Avelumab + Axitinib**

Avelumab: 10 mg/kg IV on day 1
Axitinib: 5 mg orally twice daily on days 1–14
Repeat cycle every two weeks [31].

Pembrolizumab + Axitinib

Pembrolizumab: 200 mg IV on day 1
Axitinib: 5 mg orally twice daily on days 1–21
Repeat cycle every three weeks [59].

Bevacizumab + Everolimus

Bevacizumab: 10 mg/kg IV on day 1

Everolimus: 10 mg orally once per day on days 1–14

Repeat cycle every two weeks [60].

Ipilimumab + Nivolumab

Ipilimumab: 1 mg/kg IV on day 1

Nivolumab: 3 mg/kg IV on day 1

Repeat cycle every 21 days for four cycles followed by

Nivolumab: 3 mg/kg every two weeks

Continue until progression or toxicity [61, 62].

Lenvatinib + Everolimus

Lenvatinib: 18 mg orally once daily on days 1–28

Everolimus: 5 mg orally once daily on days 1–28

Repeat cycle every four weeks and continue until disease progression or unacceptable toxic effects [63].

Bevacizumab + Interferon α -2a

Bevacizumab: 10 mg/kg IV every two weeks

Interferon α -2a: 9 million international unit subcutaneously three times per week for one year

Continue until disease progression or unacceptable toxicity [67].

9.9 Risk Factors/Possible Preventions

In general, kidney (renal) cancer develops in individuals aged 50 years and above. Males have two to three times the chances of getting kidney cancer as females [8–10, 14].

- **Smoking:** Like other types of cancer, tobacco smokers are at a higher risk of kidney cancer than nonsmokers [9].
- **Overuse of certain analgesic medications** such as aspirin, acetaminophen, and ibuprofen appears to contribute to a higher risk of developing kidney cancer.
- **Chronic kidney disease** is another contributing factor to kidney cancer. Individuals who receive long-term dialysis have been found to sometimes develop cancerous cysts in the kidneys. Early detection of these cysts is the key to the successful elimination of kidney cancer before it spreads to other parts of the body.
- **Being obese** increases a person's chance of getting kidney and other types of cancer. People are advised to maintain healthy body weight and eat a low-fat diet rich in fruit, vegetables, and whole grains. Consumption of red meat should be eliminated or minimized.
- **High blood pressure** has been linked to a higher risk of kidney cancer. This can be improved through dietary adjustments and exercise.

- **Poor sleep habits** can negatively affect the immune system. It is recommended that people get at least seven hours of quality, continuous sleep each night.
- **Toxic chemical exposure** contributes to developing kidney and other cancers, and thus should be avoided.
- **Family history:** Individuals who have a family member who has had kidney cancer are at a slightly higher risk of also suffering from this condition.
- **von Hippel-Lindau (VHL) syndrome:** VHL is a rare disease that runs in some families. It is caused by changes in the *VHL* gene and has been linked to the formation of tumors in multiple parts of the body, including clear cell RCC.

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10

Liver (Hepatocellular) Cancer

10.1 Introduction

The liver is the largest organ inside the human body, with vital functions that include assisting with digestion, removing toxins, and storing energy. Cancer that starts in the liver is called primary liver cancer, while metastatic liver cancer has originated elsewhere in the body and spread to this organ.

10.2 Gene Associated with Liver Cancer and Role of Hepatitis Infection

Liver (hepatocellular) cancer is the sixth most common cancer in the world, with 905 677 new cases diagnosed in 2020. It is the fifth most common type of cancer in males, and the ninth most common in females [1–57]. Most cases arise in individuals suffering from chronic liver disease. The incidence rate of hepatocellular cancer is rising in the United States due to the increasing frequency of liver cirrhosis caused by chronic hepatitis C infection and nonalcoholic fatty liver disease. The main cause of liver cancer is cirrhosis (Figure 10.1) due to hepatitis B, hepatitis C, or alcohol [12]. DNA changes (mutations) that turn on oncogenes or turn off tumor suppressor genes (*TP53*) are also caused by liver cancer. Certain chemicals such as aflatoxins and hepatitis viruses are known to damage the DNA in liver cells [1–12].

10.3 Liver Cancer Symptoms

- Unexplained weight loss, body wasting (also known as *cachexia*)
- Decrease in appetite
- Nausea or vomiting
- Enlarged liver (feeling a mass under the ribs on the right side)
- Enlarged spleen (feeling a mass under the ribs on the left side)
- Pain in the abdomen or in the right shoulder blade
- Swelling of legs, feet, and belly
- Fluid buildup in the belly



Figure 10.1 Healthy versus diseased liver. Source: Eranicle/Adobe Stock.

- Itching
- Yellowing of eyes and skin (jaundice)

10.4 Diagnosis

Diagnosing liver cancer is conducted through various means, including abdominal ultrasound, biopsy of liver tissue, liver function testing, imaging studies, and blood tests [14–22]. Regarding blood testing, approximately 70% of patients with liver cancer have elevated levels of *alpha-fetoprotein* (AFP), which is a protein made by the liver and yolk sac of a developing human fetus. AFP levels normally decrease soon after birth. The presence of high levels of AFP in an adult indicates the possibility of liver cancer. Liver cancer can be classified into four stages depending on how far cancer has spread (Figure 10.2).

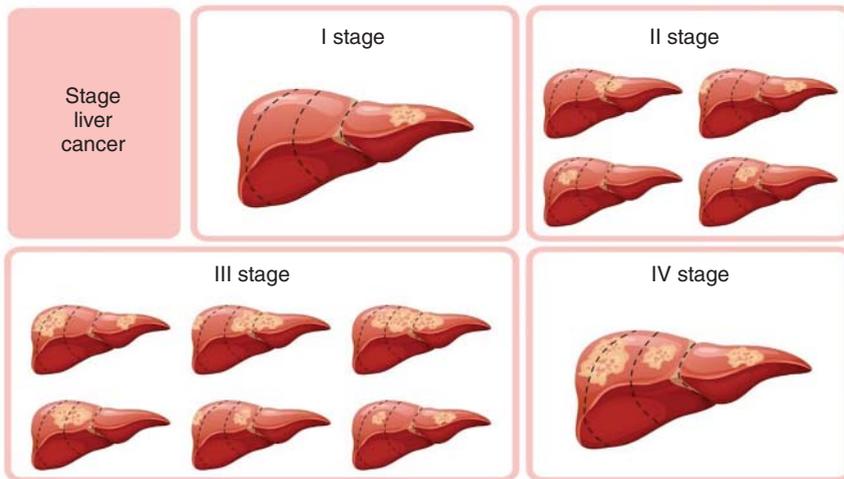


Figure 10.2 Stages of liver cancer.

10.5 Methods of Treatment

Currently, several treatment options are available for liver cancer [13, 23–74].

10.5.1 Surgery

Liver cancer can be treated sometimes with surgery to remove the part of the liver with cancer.

10.5.2 Liver Transplant

The doctor replaces the cancerous liver with a healthy liver from another person.

10.5.3 Ablation Therapies

There are various procedures in this category, which kill cancer cells in the liver without surgery. Radiofrequency ablation (RFA), microwave ablation, cryoablation (cryotherapy), and ethanol (alcohol) ablation are a few examples.

10.5.4 Embolization

In this process, the focus is on blocking the blood supply to cancer cells, thus killing them.

10.5.5 Radiation Therapy

In this procedure, high-energy radioactive rays are directed at the cancer cells from an external source in order to destroy them. The radiation, however, can also destroy normal liver cells. So, ablation and embolization are used more frequently for treating this type of cancer [38].

10.5.6 Chemotherapy

Using specialized drugs to kill cancer cells, chemotherapy can be administered by mouth or by injecting it into a vein or artery feeding the liver. The most common chemotherapy drugs for treating liver cancer are cisplatin (Platinol), capecitabine (Xeloda), doxorubicin (pegylated liposomal doxorubicin), 5-fluorouracil (5-FU), gemcitabine (Gemzar), oxaliplatin (Eloxatin), and mitoxantrone (Novantrone). Sometimes, combinations of two or three previously mentioned drugs are used.

10.5.7 Targeted Therapy

Certain medicines have been designed to specifically target various necessary cancer cell functions. For patients with advanced liver cancer, Sorafenib (Nexavar[®]) is

an oral medication that can prolong survival by blocking tumors from forming new blood vessels, which is necessary for them to grow. It also disables certain proteins found on cancer cells that normally support their growth. Other kinase inhibitors such as lenvatinib (Lenvima), regorafenib (Stivarga), pemigatinib (Pemazyre), and cabozantinib (Cabometyx) are used for treating this type of cancer as they specifically target cancer cells without killing normal cells [35–37]. Two monoclonal antibodies including bevacizumab (Avastin) and ramucirumab (Cyramza) are used for treating this type of cancer.

10.5.8 Immunotherapy

Scientists have discovered new ways to boost the human body's immune response to cancer. These drugs are new types of immune checkpoint inhibitors designed to destroy cancer cells. Pembrolizumab (Keytruda) and nivolumab (Opdivo) target the PD-1 protein; atezolizumab (Tecentriq) targets the PD-L1 protein; and ipilimumab (Yervey) targets the CTLA-4 protein. These are used more frequently for treating this type of cancer.

10.6 Treatment Regimens

Single-agent Regimens

Cabozantinib

60 mg orally once daily

Continue until disease progression or unacceptable toxicity [61]. Dose reductions to 40 mg and then to 20 mg were used to manage adverse events.

Entrectinib (for *NTRK* gene fusion-positive tumors)

600 mg orally once daily

Continue until disease progression or unacceptable toxicity [62].

Larotrectinib (for *NTRK* gene fusion-positive tumors)

100 mg orally twice daily

Continue treatment until disease progression or the occurrence of an unacceptable level of adverse events [63].

Nivolumab

240 mg IV on day 1

Repeat cycle every two weeks

Or 480 mg IV on day 1

Repeat cycle every four weeks [64].

Lenvatinib

12 mg orally daily if body weight > 60 kg on days 1–28

Or 8 mg orally daily if body weight < 60 kg on days 1–28

Repeat cycle every 28 days and continue until disease progression or unacceptable toxicity occurs [35].

Ramucirumab

8 mg/kg IV on day 1

Repeat cycle every two weeks and continue until disease progression or unacceptable toxicity [65].

Regorafenib

160 mg orally once daily on days 1–21

Repeat cycle every four weeks [36].

Sorafenib

400 mg orally twice daily on days 1–28

Repeat cycle every four weeks [66].

Pembrolizumab

200 mg IV on day 1

Repeat cycle every three weeks for two years.

May also administer 400 mg IV on day 1

Repeat cycle every six weeks up to two years or until disease progression, unacceptable toxicity, patient withdrawal, or investigator decision [67].

Combination Regimens**Atezolizumab + Bevacizumab**

Atezolizumab: 1200 mg IV infusion over 60 minutes on day 1

Bevacizumab: 15 mg/kg IV infusion over 90 minutes on day 1

Repeat cycle every three weeks [68].

Nivolumab + Ipilimumab

Nivolumab: 1 mg/kg IV over 30 minutes on day 1

Ipilimumab: 3 mg/kg IV over 90 minutes on day 1

Repeat cycle every 21 days for four cycles followed by Nivolumab 480 mg IV over 30 minutes on day 1. Repeat cycle every four weeks [64, 69].

FOLFOX-4

Oxaliplatin: 85 mg/m² IV over two hours on day 1

Leucovorin: 200 mg/m² IV infusion over two hours on days 1 and 2

5-fluorouracil: 400 mg/m² IV infusion over two hours, followed by 600 mg/m² IV continuous

infusion over 22 hours on days 1 and 2

Repeat cycle every two weeks [70, 71].

Gemcitabine + Oxaliplatin

Gemcitabine: 1000 mg/m² IV on day 1

Oxaliplatin: 100 mg/m² IV on day 2

Repeat cycle every 14 days [72].

Capecitabine + Oxaliplatin

Capecitabine: 1000 mg/m² orally twice daily on days 1–14

Oxaliplatin: 130 mg/m² IV on day 1

Repeat cycle every 21 days [73].

Gemcitabine + Cisplatin

Gemcitabine: 1250 mg/m² IV on days 1 and 8

Cisplatin: 35 mg/m² IV infusion over 30 minutes on days 1 and 8

Repeat cycle every 21 days [74].

10.7 Liver (Hepatocellular) Cancer Risk Factors/Possible Preventions

Because liver cancer usually develops in individuals with existing liver disease, it is advisable to avoid risk factors associated with hepatitis B and C and cirrhosis [13, 42–56]. In addition, it has been discovered that exposure to aflatoxins increases the risk of liver cancer. Aflatoxins are a family of toxins made by certain fungi found on crops such as corn, peanuts, cottonseed, and tree nuts.

Currently, there is a vaccine available for hepatitis B for all age groups to prevent HBV infection. Clinical trials are underway to learn more about ways to prevent all forms of cancer, including liver cancer.

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11

Lung Cancer

11.1 Introduction

The lungs are located in the rib cage and consist of two spongy organs with branching passageways that function as gas exchange sites, where blood receives oxygen for the body during inhalation and releases carbon dioxide during exhalation.

Lung cancer occurs when certain genes are damaged, or the expression of genes is altered due to a process called epigenesis (Figure 11.1). These alterations affect the cells' normal functions, including cell proliferation, programmed cell death (apoptosis), and DNA repair. As more damage occurs, so does the risk of cancer development [1–80]. Almost 80% of lung cancer is due to tobacco smoking [2, 5, 6, 10, 16]. Lung cancer in nonsmokers is caused by second-hand smoke, exposure to radon, air pollution, asbestos, diesel exhaust or certain toxic chemicals [3, 4, 9, 11] can cause lung cancers in some people who never smoke.

11.2 Genes Associated with Lung Cancer

Roughly 10–30% of lung adenocarcinomas are caused by mutation of the *K-ras* proto-oncogene [7, 12]. Nearly 4% of non-small-cell lung carcinomas are the result of a gene fusion event that gives rise to echinoderm microtubule-associated protein-like 4-anaplastic lymphoma kinase (EML4-ALK), a protein found to frequently support and maintain the malignant characteristics of cancer cells [13–15]. In addition, tumor suppressor genes can be inactivated by other complex biochemical alterations of DNA function and replication [8].

Epidermal growth factor receptor (EGFR) is a protein involved in cell proliferation, angiogenesis, apoptosis, and tumor invasion. Mutations resulting in amplification of EGFR are frequently associated with non-small-cell lung carcinoma [13, 15]. Therefore, EGFR inhibitors can be used for the treatment of lung cancers. Similarly, other genes that are mutated, including *c-MET*, *NKX2-1*, *LKB1*, *PIK3CA*, and *BRAF*, are associated with lung cancer [1, 7].

Similar to other cancers, lung cancer begins through either the activation of oncogenes or the deactivation of tumor suppressor genes. Both situations occur as a result

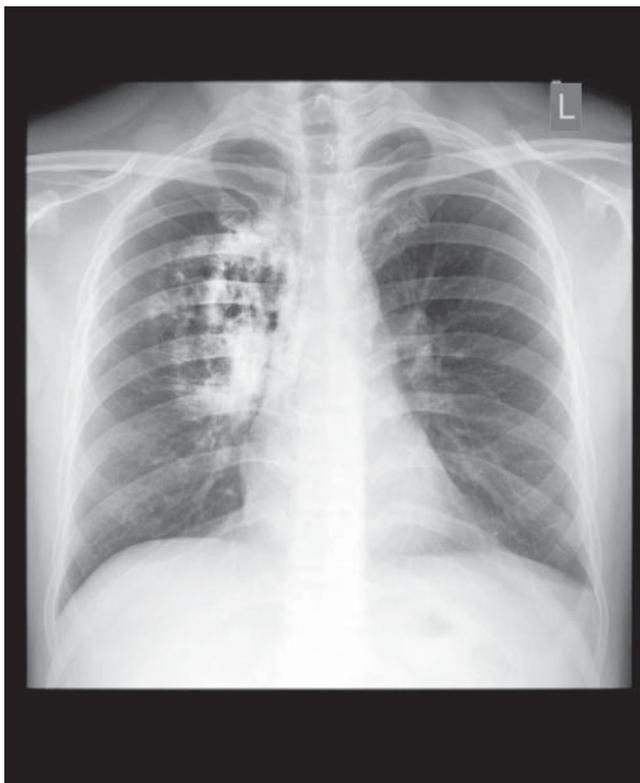


Figure 11.1 Lung cancer X-ray image.

of the cells' genetic material being exposed to carcinogens, triggering the process of cancer development [1–17].

11.3 Types of Lung Cancer

The two general types of lung cancer include:

- **Small cell lung cancer**, which is encountered almost exclusively in heavy smokers. It is less common than non-small cell lung cancer.
- **Non-small cell lung cancer** is an umbrella term for several types of lung cancers that act in a similar way. Non-small cell lung cancers include squamous cell carcinomas, adenocarcinomas, and large cell carcinomas.

11.4 Symptoms of Lung Cancer

Early-stage lung cancer typically has no symptoms. Advanced lung cancer symptoms include:

- A new cough that does not go away
- Coughing up blood (even a small amount)
- Shortness of breath
- Chest pain
- Hoarseness
- Unexplained weight loss
- Bone pain
- Headache

11.5 Diagnosis

11.5.1 Imaging Tests

An X-ray image of the lungs may reveal an abnormal mass or nodule. A computed tomography (CT) scan can reveal small lesions in the lungs that might not be detected on an X-ray. There are four staging systems for lung cancer (Figure 11.2).

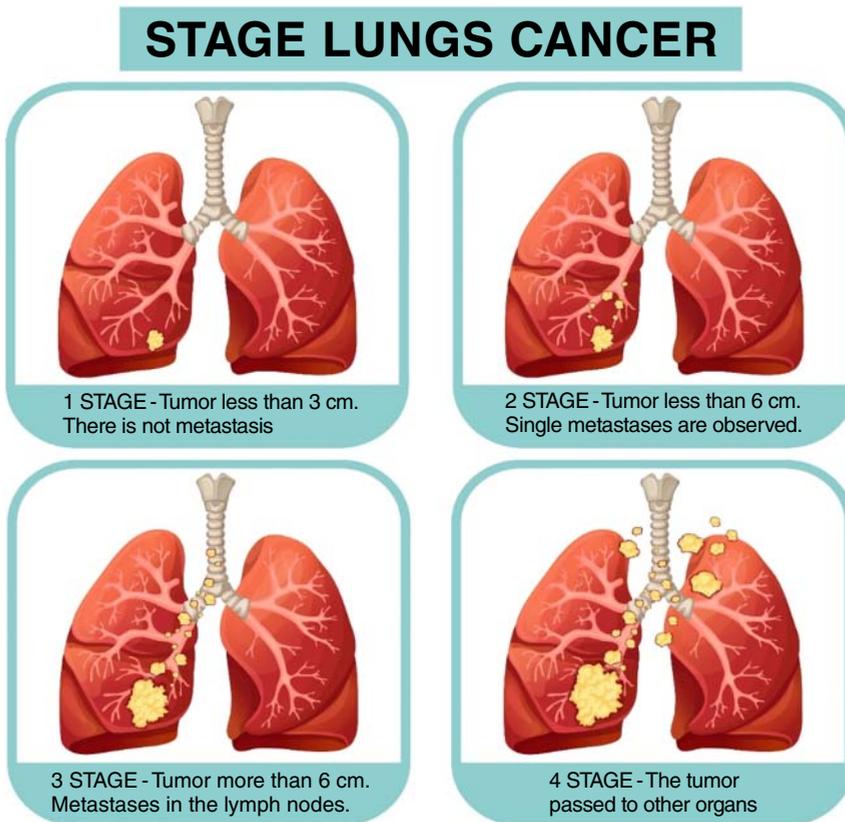


Figure 11.2 Like some other cancers, lung cancer progression is described by stages.

11.5.2 Sputum Cytology

If patients are coughing up sputum, the sputum itself can be microscopically analyzed for the presence of cancer cells.

11.5.3 Tissue Biopsy

A sample of lung tissue is obtained for analysis to check for the presence of abnormal cells.

11.6 Methods of Treatment

Currently, the following treatment options are available for lung cancer [21–145]:

11.6.1 Surgery

Physicians can remove the portion of the lung affected by cancer, as well as a margin of healthy tissues.

- Wedge resection: removal of the diseased area plus a margin of healthy tissues.
- Segmental resection: removal of a larger portion of the lung, but not an entire lobe.
- Lobectomy: refers to the removal of an entire lobe of one lung.
- Pneumonectomy: the entire diseased lung is removed.

11.6.2 Radiation Therapy

High-energy radiation is directed at the tumor in order to destroy cancer cells.

11.6.3 Chemotherapy

Drugs used to combat lung cancer are administered orally or intravenously [24, 25, 28, 31, 34, 37, 38, 41, 42, 44, 52, 66]. Specific medicines used for non-small cell lung cancer include cisplatin, carboplatin, paclitaxel (Taxol), albumin-bound paclitaxel (nab-paclitaxel, Abraxane), docetaxel (Taxotere), gemcitabine (Gemzar), vinorelbine (Navelbine), etoposide (VP-16), and pemetrexed (Alimta). For small cell lung cancer medicines used, the combinations include cisplatin and etoposide, carboplatin and etoposide, cisplatin and irinotecan, and carboplatin and irinotecan.

11.6.4 Targeted Drug Therapy

Molecular targeted therapy is designed to combat lung cancer caused by specific gene mutations. Targeted medications are specialized to work on the cancer cells

only, thus minimizing damage to healthy tissues [26, 28, 33, 39, 43–49, 53, 55, 57, 65, 66, 69–80]. An example in the case of lung cancer is EGFR-targeted therapy utilizing erlotinib (Tarceva), afatinib

(Gilotrif), gefitinib (Iressa), osimertinib (Tagrisso), and dacomitinib (Vizimpro). ALK-targeted medicines include crizotinib (Xalkori), ceritinib (Zykadia), alectinib (Alecensa), brigatinib (Alunbrig), and lorlatinib (Lorbrena); b-Raf mutation inhibitors are dabrafenib (Tafinlar) and trametinib (Mekinist); rearranged during transfection (RET) inhibitors are selpercatinib (Retevmo) and pralsetinib (Gavreto); c-MET inhibitors are capmatinib (Tabrecta) and tepotinib (Tepmetko); and neurotrophic tyrosine receptor kinase (NTRK) gene mutation inhibitors are larotrectinib (Vitrakvi) and entrectinib (Rozlytrek). All are available for treating lung cancer.

11.6.5 Immunotherapy

As with several types of cancer, immunotherapy consists of administering drug formulations designed to boost a patient's own immune system to attack cancer cells and kill them. Immune checkpoint inhibitors include nivolumab (Opdivo), pembrolizumab (Keytruda), and cemiplimab (Libtayo), which target PD-1 protein; atezolizumab (Tecentriq) and durvalumab (Imfinzi), which target PD-L1 protein; and ipilimumab (Yervoy), which targets cytotoxic T-lymphocyte-associated protein (CTLA)-4. These all are used for lung cancer [26, 28–30, 36, 64].

11.6.6 Drugs by Types of Lung Cancer

Drugs are classified by two types of lung cancer.

11.6.6.1 Drugs for Non-Small Cell Lung Cancer

Afatinib dimaleate, alectinib, atezolizumab, bevacizumab, brigatinib, capmatinib, carboplatin, cemiplimab-rwlc, ceritinib, crizotinib, dabrafenib mesylate, dacomitinib, docetaxel, doxorubicin hydrochloride, durvalumab, entrectinib, erlotinib hydrochloride, everolimus, gefitinib, gemcitabine hydrochloride, ipilimumab, lorlatinib, methotrexate sodium, necitumumab, nivolumab, osimertinib mesylate, paclitaxel, paclitaxel albumin-stabilized nanoparticle formulation, pembrolizumab, pemetrexed disodium, pralsetinib, ramucirumab, selpercatinib, sotorasib, tepotinib hydrochloride, trametinib dimethyl sulfoxide, and vinorelbine tartrate.

11.6.6.2 Drugs for Small Cell Lung Cancer

Atezolizumab, doxorubicin hydrochloride, durvalumab, etoposide, everolimus, lurbinectedin, methotrexate sodium, nivolumab, and topotecan hydrochloride.

11.7 Treatment Regimens

11.7.1 Treatment Regimens for Non-Small Cell Lung Cancer

Systemic Therapy for Advanced or Metastatic Disease

Single-agent Regimens

Afatinib

40 mg orally once daily

Continue until disease progression or unacceptable toxicity [46].

Alectinib

600 mg orally twice daily

Continue until disease progression or unacceptable toxicity [84].

Atezolizumab

1200 mg IV on day 1

Repeat cycle every three weeks [85].

Brigatinib

90 mg orally once daily on days 1–7, followed by 180 mg orally once daily on days 8–28

Repeat cycle every 28 days [75].

Capmatinib

400 mg orally twice daily

Continue until disease progression or unacceptable toxicity [70].

Cetuximab

400 mg/m² IV loading dose, then 250 mg/m² IV weekly

Repeat cycle every week.

Ceritinib

400–750 mg orally once daily

Continue until disease progression or unacceptable toxicity [57].

Crizotinib

250 mg orally twice daily

Continue until disease progression or unacceptable toxicity [49, 66, 75].

Docetaxel

75 mg/m² IV infusion over 60 minutes on day 1

Repeat cycle every 21 days [86].

Dacomitinib

45 mg orally once daily on days 1–28

Continue until disease progression or unacceptable toxicity [87].

Durvalumab

10 mg/kg IV over 60 minutes on day 1

Repeat cycle every two weeks for a maximum of 12 months [43].

Entrectinib (for *NTRK* gene fusion positive tumors)

600 mg orally once daily

Continue until disease progression or unacceptable toxicity [88].

Erlotinib (for *EGFR* mutation positive tumors)

150 mg orally once daily

Continue until disease progression or unacceptable toxicity [138].

Etoposide

50 mg/m² orally once daily on days 1–21

Repeat cycle every 21 days [115, 116].

Gefitinib

250 mg orally once daily

Continue until disease progression or unacceptable toxicity [89].

Gemcitabine

1000 mg/m² IV over 30 minutes on days 1, 8, and 15

Repeat cycle every four weeks for four to six cycles [90].

or

1250 mg/m² IV on days 1 and 8

Repeat cycle every 21 days [139].

Irinotecan

100 mg/m² IV infusion over 90 minutes on day 1

Repeat every week [106].

Lorlatinib

100 mg orally once daily on days 1–21

Repeat cycle every 21 days and continue until disease progression or unacceptable toxicity [91].

Larotrectinib (for *NTRK* gene fusion positive tumors)

100 mg orally once daily

Continue until disease progression or unacceptable toxicity [140].

Nivolumab

3 mg/kg IV over 30 minutes on day 1

Repeat cycle every two weeks [92].

or

240 mg IV every two weeks or 480 mg IV every four weeks.

Paclitaxel

225 mg/m² IV infusion over three hours on day 1

Repeat cycle every three weeks for four to six cycles.

or

Paclitaxel 80–100 mg/m² IV infusion over 60 minutes on days 1, 8, and 15

Repeat cycle every four weeks for four to six cycles [93].

Nab-paclitaxel

125 mg/m² IV on days 1, 8, and 15

Repeat cycle every four weeks [141].

Osimertinib (EGFR T790M mutation-positive tumors)

80 mg orally once daily

Continue until disease progression or unacceptable toxicity [55].

Pemetrexed

500 mg/m² IV over 10 minutes on day 1

Repeat cycle every three weeks for four to six cycles [44]. Initiate folic acid 350 µg to 1000 µg orally once daily, beginning seven days before the first dose of pemetrexed.

Administer vitamin B12, 1 mg intramuscularly, one week prior to the first dose of pemetrexed and every three cycles thereafter.

Do not substitute oral vitamin B12 for intramuscular vitamin B12.

Pembrolizumab

200 mg IV over 30 minutes on day 1

Repeat cycle every three weeks for up to two years [94].

Pralsetinib (RET fusion-positive tumors)

400 mg orally once daily

Continue until disease progression or unacceptable toxicity [95].

Selpercatinib (RET fusion-positive tumors)

120 mg orally twice daily for patients <50 kg

160 mg orally twice daily for patients >50 kg

Repeat cycle every 21 days. [96].

Sunitinib

50 mg PO once daily on days 1–28

Repeat cycle every six weeks.

Topotecan

1.5 mg/m² IV over 30 minutes once daily on days 1–5

Repeat cycle every 21 days [111, 112].

Vinorelbine

25 mg/m² IV over 5–10 minutes on day 1

Repeat cycle weekly [107].

Cemiplimab

350 mg IV on day 1

Repeat cycle every 21 days and until disease progression or unacceptable toxicity [64]

Sotorasib (KRAS G12C mutation-positive tumors)

960 mg orally daily

Continue treatment until disease progression or unacceptable toxicity [142].

Combination Regimens**Docetaxel + Cisplatin**

Docetaxel: 75 mg/m² IV over 60 minutes on day 1, followed by

Cisplatin: 75 mg/m² IV over 60 minutes on day 1

Repeat cycle every three weeks for four to six cycles [97].

Etoposide + Cisplatin

Etoposide: 100 mg/m² IV over 60 minutes daily on days 1–3

Cisplatin: 60 mg/m² IV over 60 minutes on day 1

Repeat cycle every three weeks for four to six cycles [98].

Gemcitabine + Cisplatin

Gemcitabine: 1000 mg/m² IV over 30 minutes on days 1, 8, and 15

Cisplatin: 100 mg/m² IV over 60 minutes on day 1

Repeat cycle every four weeks for four to six cycles [117].

Cisplatin + Paclitaxel

Paclitaxel: 135 mg/m² IV infusion over 24 hours on day 1

Cisplatin: 75 mg/m² IV over 60 minutes on day 2

Repeat cycle every three weeks [117].

Cisplatin + Pemetrexed

Pemetrexed: 500 mg/m² IV over 10 minutes on day 1

Cisplatin: 75 mg/m² IV over 60 minutes on day 1

Repeat cycle every three weeks [99].

Initiate folic acid 350 µg to 1000 µg orally once daily, beginning seven days before the first dose of pemetrexed. Administer vitamin B12, 1 mg intramuscularly, one week prior to the first dose of pemetrexed and every three cycles thereafter.

Do not substitute oral vitamin B12 for intramuscular vitamin B12.

Cisplatin + Vinblastine

Cisplatin: 100 mg/m² IV over 60 minutes on day 1

Vinblastine: 4 mg/m² IV on days 1, 8, 15, 22, and 29

Repeat cycle every four weeks [37].

Cisplatin + Vinorelbine

Cisplatin: 100 mg/m² IV over 60 minutes on day 1

Vinorelbine: 25 mg/m² IV over 5–10 minutes on days 1, 8, 15, and 22

Repeat cycle every four weeks for four cycles [42].

Docetaxel + Carboplatin

Docetaxel: 75 mg/m² IV over 60 minutes on day 1

Carboplatin: Area under curve (AUC) of 6, IV over 30 minutes on day 1

Repeat cycle every three weeks for four to six cycles [97].

Gemcitabine + Carboplatin

Gemcitabine: 1000 mg/m² IV over 30 minutes on days 1 and 8

Carboplatin: AUC of 5, IV over 30 minutes on day 1

Repeat cycle every four weeks [118].

Paclitaxel + Carboplatin

Paclitaxel: 200 mg/m² IV over three hours on day 1

Carboplatin: AUC of 6, IV over 30 minutes on day 1

Repeat cycles every three weeks for four to six cycles [117].

Carboplatin + Albumin-Bound Paclitaxel (Nab-Paclitaxel)

Carboplatin: AUC of 6, IV over 30 minutes on day 1

Albumin-bound paclitaxel: 100 mg/m² IV over 30 minutes on day 1, 8, and 15

Repeat cycles every 21 days [100].

Carboplatin + Vinorelbine

Carboplatin: AUC of 6, IV over 30 minutes on day 1

Vinorelbine: 25 mg/m² IV over 5–10 minutes on days 1 and 8

Repeat cycle every four weeks [119].

Docetaxel + Ramucirumab

Docetaxel: 75 mg/m² IV over 60 minutes on day 1

Ramucirumab: 10 mg/kg IV over 60 minutes on day 1

Repeat cycle every three weeks [101].

Dabrafenib + Trametinib

Dabrafenib: 150 mg orally twice daily

Trametinib: 2 mg orally once daily

Continue until disease progression or unacceptable adverse events or withdrawal of consent [102].

Erlotinib + Ramucirumab

Erlotinib: 150 mg orally once daily on days 1–14

Ramucirumab: 10 mg/kg IV over 60 minutes on day 1

Repeat cycle every two weeks [103].

Ipilimumab + Nivolumab

Ipilimumab: 1 mg/kg IV over 30 minutes on day 1

Nivolumab: 3 mg/kg IV over 30 minutes on days 1, 15, and 29

Repeat cycle every six weeks for a maximum of two years [73].

Cisplatin + Cetuximab + Vinorelbine

Cisplatin: 80 mg/m² IV infusion over one hour on day 1

Vinorelbine: 25 mg/m² IV over 10 minutes on days 1 and 8

Cetuximab: 400 mg/m² IV over 10 minutes' loading dose, then 250 mg/m² IV weekly

Repeat cycle every three weeks for six cycles [121].

Carboplatin + Paclitaxel + Bevacizumab

Carboplatin: AUC of 6, IV over 30 minutes on day 1
 Paclitaxel: 200 mg/m² IV over three hours on day 1
 Bevacizumab: 15 mg/kg IV on day 1
 Repeat cycle every three weeks for six cycles [104].

Carboplatin + Paclitaxel + Pembrolizumab

Carboplatin: AUC of 6, IV over 30 minutes on day 1
 Paclitaxel: 200 mg/m² IV over three hours on day 1
 Pembrolizumab: 200 mg IV over 30 minutes on day 1
 Repeat cycle every three weeks for four cycles [72].

Carboplatin + Nab-Paclitaxel + Pembrolizumab

Carboplatin: AUC of 6, IV over 30 minutes on day 1
 Nab-Paclitaxel: 100 mg/m² IV over 30 minutes on days 1, 8, and 15
 Pembrolizumab: 200 mg IV over 30 minutes on day 1
 Repeat cycle every three weeks for four cycles [72, 105].

Cisplatin + Gemcitabine + Bevacizumab

Cisplatin: 80 mg/m² IV over 60 minutes on day 1
 Gemcitabine: 1250 mg/m² IV over 30 minutes on days 1 and 8
 Bevacizumab: 7 mg/kg or 15 mg/kg IV on day 1
 Repeat cycle every 21 days for six cycles [122].

Cisplatin + Gemcitabine + Necitumumab

Cisplatin: 75 mg/m² IV over 120 minutes on day 1
 Gemcitabine: 1250 mg/m² IV over 30 minutes on days 1 and 8
 Necitumumab: 800 mg IV infusion over 50 minutes on days 1 and 8
 Repeat cycle every three weeks and continue until disease progression or intolerable toxic side effects occur [123].

Cisplatin + Etoposide + Docetaxel

Cisplatin: 50 mg/m² IV over 60 minutes on days 1, 8, 29, and 36
 Etoposide: 50 mg/m² IV over 60 minutes on days 1–5 and 29–33
 Concurrent thoracic radiation total dose of 61 Gy, four to six weeks after consolidation docetaxel starts
 Docetaxel: 75 mg/m² IV over 60 minutes on day 1
 Repeat cycle every three weeks [124].

Cisplatin + Pemetrexed + Pembrolizumab

Cisplatin: 75 mg/m² IV over 60 minutes on day 1
 Pemetrexed: 500 mg/m² IV over 10 minutes on day 1
 Pembrolizumab: 200 mg IV over 30 minutes on day 1
 Repeat cycle every three weeks for four cycles followed by pemetrexed 500 mg/m² every three weeks. All the patients should receive premedication with folic acid, vitamin B12, and glucocorticoids according to local guidelines for pemetrexed use [77].

Carboplatin + Pemetrexed + Bevacizumab

Carboplatin: AUC of 6, IV over 30 minutes on day 1

Pemetrexed: 500 mg/m² IV over 10 minutes on day 1

Bevacizumab: 15 mg/kg IV on day 1

Repeat cycle every three weeks with premedication with folic acid, vitamin B12, and glucocorticoids according to local guidelines for pemetrexed use [125].

Carboplatin + Pemetrexed + Pembrolizumab

Carboplatin: AUC of 5, IV over 30 minutes on day 1

Pemetrexed: 500 mg/m² IV over 10 minutes on day 1

Pembrolizumab: 200 mg IV over 30 minutes on day 1

Repeat cycle every three weeks with premedication with folic acid, vitamin B12, and glucocorticoids according to local guidelines for pemetrexed use [77].

Atezolizumab + Paclitaxel + Carboplatin

Atezolizumab: 1200 mg IV on day 1

Paclitaxel: 200 mg/m² IV over three hours on day 1

Carboplatin: AUC of 6, IV over 30 minutes on day 1

Repeat cycle every three weeks [126].

Atezolizumab + Bevacizumab + Paclitaxel + Carboplatin

Atezolizumab: 1200 mg IV on day 1

Bevacizumab: 15 mg/kg IV on day 1

Paclitaxel: 200 mg/m² IV over 3 hours on day 1

Carboplatin: AUC of 6, IV over 30 minutes on day 1

Repeat cycle every three weeks [100, 126].

11.7.2 Treatment Regimens for Small Cell Lung Cancer**Single-agent Regimens****Docetaxel**

100 mg/m² IV over 60 minutes on day 1

Repeat cycle every three weeks [127].

Etoposide

50 mg/m² orally once on days 1–5

Repeat cycle every four weeks [116].

Gemcitabine

1000 mg/m² orally once on days 1, 8, and 15

Repeat cycle every four weeks [128].

Irinotecan

100 mg/m² IV infusion over 90 minutes on days 1, 8, 15, and 22

Repeat cycle every four weeks [106].

Lurbinectedin

3.2 mg/m² IV infusion over one hour on day 1

Repeat cycle every three weeks [33].

Nivolumab

240 mg IV over 30 minutes on day 1 or 3 mg/Kg IV
Repeat cycle every two weeks [129].

Paclitaxel

80–100 mg/m² IV over 60 minutes on days 1, 8, and 15
Repeat cycle every four weeks for four to six cycles [93, 143].

Pembrolizumab

200 mg IV over 30 minutes every three weeks or 10 mg/Kg every two weeks
Repeat cycle every three weeks for up to two years [130].

Topotecan

1.5 mg/m² IV daily over 30 minutes on days 1–5
Repeat cycle every three weeks [111–114].

Vinorelbine

25–30 mg/m² IV over 10 minutes on day 1
Repeat cycle every seven days [107].

Ifosfamide

5 g/m² IV with Mesna protection on day 1
Repeat cycle every 21 days [144].

Temozolomide

75 mg/m² orally one daily on days 1–21
Repeat cycle every 28 days [145]

Combination Regimens**Cisplatin + Etoposide**

Cisplatin: 60–80 mg/m² IV over 60 minutes on day 1
Etoposide: 80–120 mg/m² IV over 60 minutes on days 1–3
Repeat cycle every three weeks for four to six cycles [108].

Carboplatin + Etoposide

Carboplatin: AUC of 6, IV over 30 minutes on day 1
Etoposide: 100 mg/m² IV over 60 minutes on days 1–3
Repeat cycle every four weeks for four to six cycles [109].

Carboplatin + Irinotecan

Carboplatin: AUC of 5, IV infusion over 60 minutes on day 1
Irinotecan: 50 mg/m² IV over 30 minutes on days 1, 8, and 15
Repeat cycle every four weeks [110].

Cisplatin + Irinotecan

Cisplatin: 60 mg/m² IV over 60 minutes on day 1
Irinotecan: 60 mg/m² IV over 90 minutes on days 1, 8, and 15
Repeat cycle every four weeks [131].

Topotecan + Cisplatin

Topotecan: 1.7 mg/m² orally once daily on days 1–5

Cisplatin: 80 mg/m² IV over 60 minutes on day 5

Repeat cycle every three weeks for four cycles [132].

Carboplatin + Paclitaxel

Carboplatin: AUC of 2, IV over 30 minutes on days 1, 8, and 15

Paclitaxel: 80 mg/m² IV over three hours on days 1, 8, and 15

Repeat cycle every four weeks for up to six cycles [133].

Nivolumab + Ipilimumab

Nivolumab: 1 mg/kg IV over 30 minutes on days 1, 15, and 29

Ipilimumab: 3 mg/kg IV over 90 minutes on day 1

Repeat cycle every three weeks [134, 135].

Cyclophosphamide + Doxorubicin + Vincristine

Cyclophosphamide: 1000 mg/m² IV over 60 minutes on day 1

Doxorubicin (Adriamycin): 45 mg/m² IV on day 1

Vincristine: 1 mg/m² IV (maximum 2 mg) over 10 minutes on day 1 (maximum)

Repeat cycle every three weeks [111].

Cyclophosphamide + Doxorubicin + Etoposide

Cyclophosphamide: 1000 mg/m² IV over 60 minutes on day 1

Doxorubicin (Adriamycin): 45 mg/m² IV on day 1

Etoposide: 50 mg/m² IV over 60 minutes on days 1–5

Repeat cycle every three weeks [136].

Carboplatin + Paclitaxel + Etoposide

Carboplatin: AUC of 6, IV infusion over 30 minutes on day 1

Paclitaxel: 200 mg/m² IV infusion over 60 minutes on day 1

Etoposide: 50–100 mg/m² IV over 60 minutes on days 1–10

Repeat cycle every three weeks [137].

Atezolizumab + Carboplatin + Etoposide

Atezolizumab: 1200 mg IV on day 1

Carboplatin: AUC of 5, IV over 30 minutes on day 1

Etoposide: 50 mg/m² IV over 60 minutes on days 1–3

Repeat cycle every 21 days for four cycles [76].

Durvalumab + Carboplatin + Etoposide

Durvalumab: 1500 mg IV on day 1

Carboplatin: AUC of 5, IV over 30 minutes on day 1 (or Cisplatin 75–80 mg/m² IV on day 1)

Etoposide: 100 mg/m² IV over 60 minutes on days 1–3

Repeat cycle every three weeks for four cycles [65], followed by maintenance durvalumab 1500 mg every four weeks.

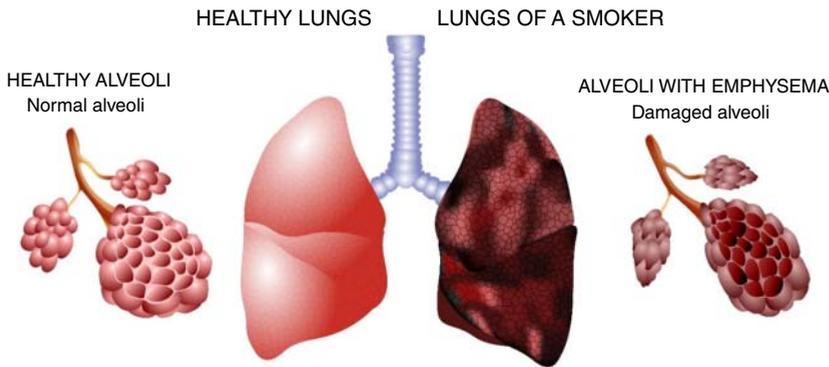


Figure 11.3 Effects of smoking on healthy lungs.

11.8 Risk Factors and Possible Preventions

Do not smoke. Because smoking is a major environmental risk factor for developing lung cancer, it should be avoided entirely (Figure 11.3). People who have never smoked should avoid starting, as nicotine is an addictive substance, and smoking becomes increasingly difficult to stop once it becomes a habit. Children should be advised of the risks of cigarette smoking starting at an early age. Secondhand smoke from others is also harmful. So, individuals should seek a smoke-free environment whether at work or in bars and restaurants.

Those who have smoked for years, however, can still reduce their risk of lung cancer by quitting. Information about strategies and programs for quitting are available through physicians and in many community health venues.

Besides this, exposure to toxic chemicals should be avoided, whether at work or at home. Eliminating this type of exposure is preventable if people learn to be aware of the substances they use or are around daily. Particularly in the case of lung cancer, being around asbestos fibers can be deadly (see Chapter 13 on Mesothelioma).

Other recommendations, which apply to lowering the risk of all types of cancer, are eating a diet rich in fruits and vegetables, and commitment to regular exercise [60–63].

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12

Melanoma (Skin Cancer)

12.1 Introduction

Melanoma is the most aggressive and dangerous form of skin cancer. Melanomas develop in pigment-producing cells called melanocytes, located in the basal layer of the epidermis in the skin [1–22]. Cancerous growth arises due to unrepaired DNA damage in skin cells caused by ultraviolet radiation, which leads to mutations causing the cells to grow rapidly and develop into malignant tumors [1–94]. Melanomas look similar to moles, and some originate from moles. Most melanomas are black or brown, but they can also be skin-colored, pink, red, purple, blue, or white (Figure 12.1).

12.2 Genes Associated with Melanoma

Familial malignant melanoma refers to families in which two or more first-degree relatives, like a parent, sibling, and/or a child, have melanoma skin cancer. In fact, approximately 8% of newly diagnosed melanomas are in patients having a first-degree relative with melanoma. Several genes have been primarily associated with melanoma. About half of all diagnosed melanomas have a mutation in a gene called *BRAF*, which, when mutated, is “switched on” to support uncontrolled cell growth and the development of cancer. Other genes in which mutations have been linked to familial melanoma are *p53*, *CDKN2A*, *NRAS*, *CDKN2A*, *NF1*, *MC1R*, *ALK*, *RET*, *ROS1*, *NTRK1*, *NTRK3*, *MET*, *CDK4*, *BRCA2*, and others [8–19].

12.3 Types of Melanoma

Here different types of melanoma are described.

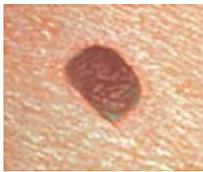
12.3.1 Superficial Spreading Melanoma

This is the most common type, often developing on the trunk or limbs. The cells tend to grow slowly at first, before spreading across the surface of the skin.



Figure 12.1 (a–c) Different types of malignant melanoma appearance on skin. Source: (a) dream@do/Adobe Stock (b) Stefano Garau/Adobe Stock (c) CDC Public Health Image Library/CDC (Centers for Disease Control and Prevention).

(a)



BENIGN

(b)



MALIGNANT

(c)

12.3.2 Nodular Melanoma

This is the second most common type of melanoma, developing on the trunk, head, or neck. It tends to grow more quickly than other types, turning red rather than black as it develops.

12.3.3 Lentigo Maligna Melanoma

Usually seen in older people, this rare type of melanoma is evidenced particularly in parts of the body that have been exposed to the sun over many years. It begins as a Hutchinson's freckle, or lentigo maligna, which looks like a stain on the skin. It generally grows slowly and is less dangerous than other types.

12.3.4 Acral Lentiginous Melanoma

It is the rarest type of melanoma, which usually arises on the palms of the hands, soles of the feet, or under the nails. It is found more commonly in people with darker skin, and it is not linked to sun exposure.

12.4 Stages of Malignant Melanoma

Stage 0: The cancer is only in the outermost layer of skin and is known as melanoma in situ.

Stage 1: The cancer is up to 2 millimeters (mm) thick. It has not extended to lymph nodes or other sites, and it may or may not have ulcerated the skin (ulceration means healthy skin tissue has been lost).

Stage 2: The cancer is at least 1.01 mm thick and it may be thicker than 4 mm. It may or may not be ulcerated, and it has not yet spread to lymph nodes or other parts.

Stage 3: The cancer may be thicker than 4 mm and has extended to one or more lymph nodes or nearby lymphatic channels, but not too distant sites.

Stage 4: The cancer has reached distant lymph nodes or organs, such as the brain, lungs, or liver.

12.5 Symptoms of Melanoma Cancer

- Skin changes, such as a new spot or mole, or change in color, shape, or size of a current spot or mole
- Skin sore that fails to heal
- Spot or sore that becomes painful, itchy, or tender, or which bleeds
- Spot or lump that looks shiny, waxy, smooth, or pale
- Firm, red lump that bleeds or appears ulcerated or crusty
- Flat, red spot that is rough, dry, or scaly

12.6 Diagnosis

Diagnosis of malignant melanoma proceeds in two steps:

Step 1: Biopsy/Tissue Analysis

Step 2: Lymph Node Status – this is accomplished through a variety of imaging tests.

Early detection of malignant melanoma is the most powerful factor in its successful elimination. The **ABCDE examination** of skin moles (Figure 12.2) is an effective guide in early detection, describing five simple characteristics in the appearance of cancerous-looking spots or moles:

12.6.1 Asymmetric

Normal moles are often round and symmetrical, whereas one side of a cancerous mole is likely to look different from the other side, i.e. not round or symmetrical.

12.6.2 Border

The edges of cancerous moles are likely to be irregular, i.e. ragged, notched, or blurred, rather than smooth.

12.6.3 Color

Melanomas tend not to be uniform in color, but instead contain various shades and colors, such as black, brown, tan, and sometimes even white or blue.

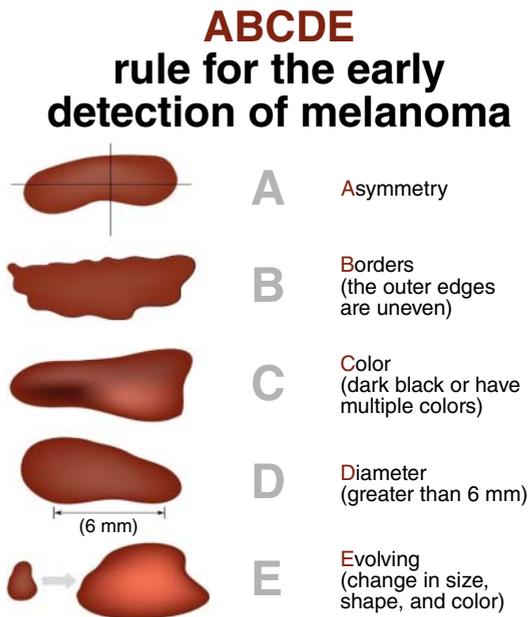


Figure 12.2 Checking for melanoma...ABCDE.

12.6.4 Diameter

Change in the size of the mole, or a mole that is larger than a normal mole (more than .25" in diameter) can indicate skin cancer.

12.6.5 Evolving

Change in a mole's appearance over a period of weeks or months can also be a sign of skin cancer.

12.7 Methods of Treatment

Several methods are available for treating melanoma [26–111].

12.7.1 Surgery

The tumor and some of the normal tissues around it are removed. A biopsy is often performed at the same time.

12.7.2 Radiation

High-energy radiations such as X-rays are used to kill cancer cells.

12.7.3 Chemotherapy

Medication designed to kill cancer cells is systemically administered orally or intravenously. Several FDA-approved chemotherapy agents for use with melanoma skin

cancer are dacarbazine (also called DTIC), temozolomide, nab-paclitaxel, paclitaxel, cisplatin, and carboplatin.

12.7.4 Targeted Therapy

Medication therapy targets tumor cells without damaging normal cells. The following targeted therapies are currently approved by the FDA for the treatment of melanoma that is positive for the B-RAF mutation: dabrafenib (Tafinlar), encorafenib ((Braftovi), and vemurafenib (Zelboraf). MEK inhibitors used to treat melanoma skin cancer include binimetinib (Mektovi), cobimetinib (Cotellic), and trametinib (Mekinist).

12.7.5 Immunotherapy

Drug formulations designed to boost a patient's own immune system are administered singly or in combination to bolster the body's own ability to attack and destroy cancer cells. FDA-approved immunotherapy agents for melanoma treatment include talimogene laherparepvec (T-VEC or trade name Imlygic), ipilimumab (Yervoy), nivolumab (Opdivo), pembrolizumab (Keytruda), atezolizumab (Tecentriq), interleukin-2 (IL-2), interferon alpha 2-b, and peginterferon alfa-2b.

12.7.6 Photodynamic Therapy

It uses a combination of light and drugs, and radiation is used in rare instances.

Several clinical trials are underway regarding the treatment of melanoma skin cancer with the goal of developing more medications for chemotherapy, immunotherapy, and targeted therapy.

12.8 Drugs for Other Types of Skin Cancer

Other common skin cancers are basal cell carcinoma, cutaneous squamous cell carcinoma, and Merkel cell carcinoma.

12.8.1 Drugs for Basal Cell Carcinoma

Cemiplimab-rwlc, 5-fluorouracil-topical, imiquimod, sonidegib, and vismodegib.

12.8.2 Drugs for Cutaneous Squamous Cell Carcinoma

Cemiplimab-rwlc and pembrolizumab.

12.8.3 Drugs for Merkel Cell Carcinoma

Avelumab and pembrolizumab.

12.8.4 Drugs for Kaposi Sarcoma

Bleomycin, liposomal doxorubicin (Doxil), liposomal daunorubicin (DaunoXome), recombinant interferon alfa-2b, paclitaxel, nab-paclitaxel (Abraxane), gemcitabine (Gemzar), vinorelbine (Navelbine), pomalidomide, vinblastine sulfate (Velban), vincristine (Oncovin), etoposide (VP-16), thalidomide (Thalomid), pomalidomide (Pomalyst), and lenalidomide (Revlimid).

12.9 Treatment Regimens

These regimens are provided as references only to the latest treatment strategies and educational purposes [43–111]. Clinicians must choose and verify treatment options based on the individual patient's physical condition.

Adjuvant Therapy

Single-agent Regimens

Interferon alfa-2b

20 million IU/m² IV daily for four weeks, then 10 million IU/m² SC three times weekly for 48 weeks. The total treatment is for one year [43].

Ipilimumab

10 mg/kg IV on day 1

Repeat cycle every three weeks for 4 doses followed by 10 mg/kg on day 1 every 12 weeks for three years [88].

Nivolumab

3 mg/kg IV on day 1

Repeat cycle every two weeks [76].

Peg-interferon alfa-2b

6 µg/kg SC weekly for eight weeks followed by 3 µg/kg SC weekly for up to five years [95].

Pembrolizumab

200 mg IV on day 1

Repeat cycle every three weeks for up to one year [72].

Combination Regimens

Dabrafenib + Trametinib

Dabrafenib: 150 mg orally twice daily

Trametinib: 2 mg orally once daily

Continue treatment for up to one year [75].

Systemic Therapy for Advanced or Unresectable or Metastatic Melanoma

Single-agent Regimens

Binimetinib (for *NRAS*-mutated tumors)

45 mg orally twice daily

Continue until disease progression or unacceptable toxicity [92].

Dabrafenib (for *BRAF V600E* mutated tumors)

150 mg orally twice daily

Continue until disease progression or unacceptable toxicity [96].

Dacarbazine

250 mg/m² IV on days 1–5

Repeat cycle every three weeks [97].

Or 1000 mg/m² IV every three weeks [92].

Entrectinib (for *NTRK* gene fusion-positive tumors)

600 mg orally twice daily

Continue until disease progression or unacceptable toxicity [91].

Interleukin-2 (Aldesleukin)

600 000 or 720 000 IU/kg IV infusion over 15 minutes every eight hours on days 1–5 and 15–19

Repeat cycle in 6–12 weeks' interval [98].

Interferon alfa-2b

20 million IU/m² IM three times per week

Continue up to 12 weeks [43, 49, 99].

Imatinib

400 mg orally twice daily

Continue until disease progression or intolerable toxicity [80].

Ipilimumab

3 mg/kg IV over 90 min on day 1

Repeat cycle every three weeks for a total of four cycles [90].

Larotrectinib (for *NTRK* gene fusion-positive tumors)

100 mg orally twice daily

Continue until disease progression or unacceptable toxicity [91].

Nivolumab

3 mg/kg IV on day 1

Repeat cycle every two weeks [58].

Pembrolizumab

10 mg/kg IV infusion over 30 minutes on day 1

Repeat cycle every three weeks and continue until disease progression or unacceptable toxicity [46].

Trametinib (for *BRAF V600E* or *V600K* mutations)

2 mg orally once daily

Continue treatment until disease progression or unacceptable toxicity [100].

Temozolomide200 mg/m² orally once daily on days 1–5

Repeat cycle every 28 days [101].

Vemurafenib (for *BRAF V600E* mutation, not indicated for wild-type *BRAF* melanoma)

960 mg orally twice daily

Continue treatment until disease progression or unacceptable toxicity [102].

Paclitaxel250 mg/m² IV continuous infusion for 24 hours

Repeat cycle every 21 days [106].

Albumin-bound paclitaxel100 mg/m² IV on day 1 (in previously treated patients) or 150 mg/m² IV on day 1 (in chemotherapy-naïve patients)

Repeat cycle every week for four cycles [107, 108].

Systemic Therapy for Advanced or Unresectable or Metastatic Melanoma**Combination Regimens****Cobimetinib + Vemurafenib**

Cobimetinib: 60 mg orally once daily on days 1–21

Vemurafenib: 960 mg orally twice daily on days 1–28

Repeat cycle every 28 days [93].

Dabrafenib + Trametinib

Dabrafenib: 150 mg orally twice daily

Trametinib: 2 mg orally once daily

Repeat cycle every 28 days [15].

Encorafenib + Binimetinib

Encorafenib: 300 mg orally once daily

Binimetinib: 45 mg orally twice daily

Continue treatment until disease progression or unacceptable toxicity [94].

Nivolumab + Ipilimumab

Nivolumab: 1 mg/kg IV infusion over a period of 60 minutes on day 1

Ipilimumab: 3 mg/kg IV over 90 minutes on day 1

Repeat cycle every 21 days for four cycles followed by the maintenance phase

Nivolumab: 3 mg /kg IV over 60 minutes on day 1 and ipilimumab was discontinued
 Repeat cycle every two weeks until disease progression or unacceptable toxicity [58, 89].

Temozolomide + Thalidomide

Temozolomide: 75 mg/m² orally once daily for six weeks
 Thalidomide: 200 mg orally once daily for six weeks with dose escalation to 400 mg/d for patients < 70 years old, or 100 mg/d with dose escalation to 250 mg/d for patients ≥ 70 years old
 Repeat cycle every eight weeks (two weeks' rest) [103].

Interferon alfa-2b + Dacarbazine

Interferon alfa-2b: 15 million IU/m² IV on days 1–5, 8–12, and 15–19 as induction therapy followed by
 Interferon alfa-2b: 10 million IU/m² SC 3 times weekly after induction therapy
 Dacarbazine: 200 mg/m² IV on days 22–26
 Repeat cycle every 28 days [104].

Atezolizumab + Cobimetinib + Vemurafenib

Atezolizumab: 840 mg IV on day 1
 Cobimetinib: 60 mg orally once daily on days 1–21
 Vemurafenib: 720 mg orally twice daily on days 1–21
 Repeat cycle every 28 days [57].

Dacarbazine + Carmustine + Cisplatin

Dacarbazine: 220 mg/m² IV over 60 minutes on days 1–3
 Carmustine: 150 mg/m² IV over three hours on day 1
 Cisplatin: 25 mg/m² IV over 45 minutes on days 1–3
 Repeat cycle with dacarbazine and cisplatin every 21 days and carmustine every 42 days [105].

Carboplatin + Paclitaxel

Carboplatin: AUC of 6, IV on days 1, 8, and 15
 Paclitaxel: 100 mg/m² IV on days 1, 8, and 15 or 225 mg/m² every three weeks
 Repeat cycle every 28 days [109–111].

12.10 Melanoma Risk Factors

As with all cancers, research is ongoing into the causes of melanoma. The following factors are linked with an increased chance of skin cancer (Source: Based on [55–63]):

- High freckle density or tendency for freckles to appear after sun exposure
- High number of moles
- Five or more atypical moles
- Presence of actinic lentigines, which are small, grayish-brown spots (also known as liver spots, sun spots, or age spots)
- Giant congenital melanocytic nevi, which are brown skin marks present at birth, otherwise known as birthmarks
- Pale skin that does not tan easily and burns, plus light-colored eyes
- Red or light-colored hair
- High sun exposure, particularly if it produces blistering sunburn, and especially if sun exposure is intermittent rather than regular
- Age (risk increases with age)
- Family history of melanoma
- Personal history of melanoma
- Persons having received an organ transplant
- Genetic risk factors
- Weakened immune system

Of these, only high sun exposure and sunburn are avoidable.

12.11 Possible Prevention

According to the World Health Organization (WHO), almost 60 000 early deaths occur each year worldwide due to excessive exposure to the sun's ultraviolet (UV) radiation [62–70]. An estimated 48 000 of these deaths are from malignant melanoma.

Avoiding overexposure to the sun and preventing sunburn can significantly lower the risk of skin cancer [62–70]. Tanning beds are also a source of damaging UV rays.

12.11.1 Sun Protection Tips

- Avoid sunburn.
- Wear clothes that protect against the sun.
- Use sunscreen with a minimum sun protection factor (SPF) of 15, but preferably SPF 20–30, with 4- or 5-star UVA protection.
- Liberally apply sunscreen about one-half hour before going outside, and reapply after one-half hour.
- Reapply sunscreen every two hours and after swimming to maintain adequate protection.
- Avoid the highest sun intensity between 10 am and 4 pm.
- Protect children by keeping them in the shade, dressing them in protective clothing, and applying SPF 50+ sunscreen.
- Keep infants out of direct sunlight.



Figure 12.3 Sun protection.

Wearing sunscreen is not a reason to spend longer in the sun. Sun exposure should still be limited, where possible. People who work outdoors should take precautions to minimize exposure.

12.11.2 What about Vitamin D?

In spite of the dangers from sun overexposure, it remains important to get some sun so that the body can produce vitamin D, which is an important nutrient and prevents such diseases as rickets and osteomalacia. The time it takes in the sun-light for our bodies to produce a sufficient amount of vitamin D is less than the time it takes to get sunburnt. It is possible, therefore, to enjoy the sun safely and maintain optimal vitamin D levels without dramatically increasing the risk of skin cancer (Figure 12.3).

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13

Mesothelioma

13.1 Introduction

Malignant mesothelioma is a very rare, aggressive form of cancer caused by the inhalation of asbestos fibers. It begins within a tissue called the mesothelium, which lines many of the internal organs [1–45]. The most common area affected by mesothelioma is the lining of the lungs (Figure 13.1) and chest wall [1–3]. Less commonly, the disease begins in the lining of the abdomen, heart, or testes.

13.2 Genes Associated with Mesothelioma

Mutations of genes have been linked to mesothelioma including *BAP1*, *PALB2*, *BRCA1*, *FANCI*, *ATM*, *SLX4*, *BRCA2*, *FANCC*, *FANCF*, *PMS1*, and *XP*. These genes are also involved in DNA repair pathways [2–8].

13.3 Types of Mesothelioma Cancers

There are four primary types of mesothelioma cancers, based on the location where a tumor first develops (Figure 13.2).

1. **Pleural Mesothelioma** (Lungs)
2. **Peritoneal Mesothelioma** (Abdomen)
3. **Pericardial Mesothelioma** (Heart)
4. **Testicular Mesothelioma** (Testes; very rare)

13.4 Mesothelioma Cancer Symptoms

Different mesothelioma cancers have some common and uncommon symptoms.

13.4.1 Symptoms for Pleural Mesothelioma

- Faint or harsh breathing
- Dry cough or wheezing

Process of mesothelioma cause from asbestos

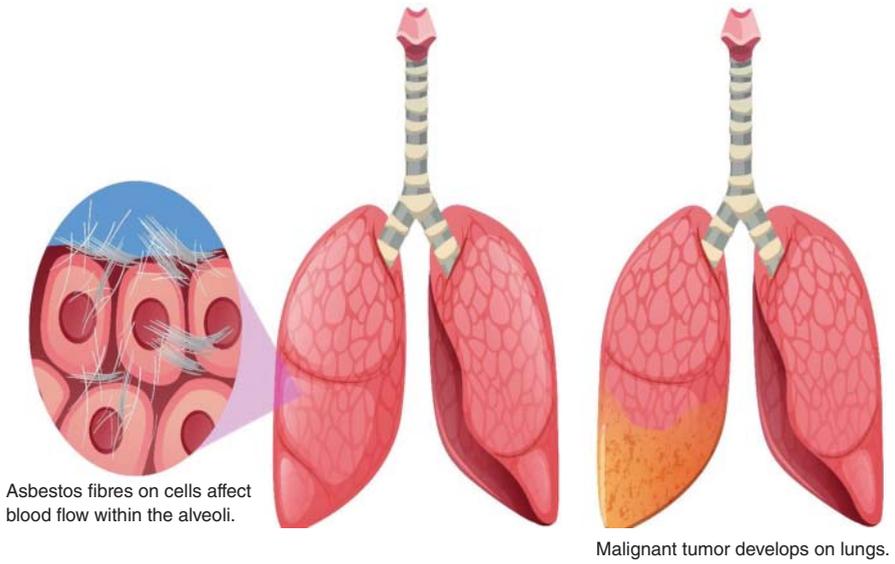


Figure 13.1 Mesothelioma from inhalation of asbestos fibers.

Mesothelioma types

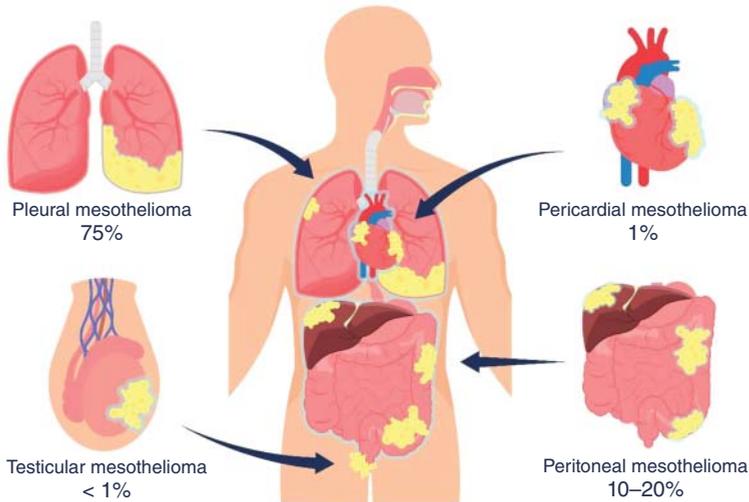


Figure 13.2 Types of mesothelioma.

- Coughing up blood
- Body aches
- Blood clotting disorder
- Chest pains
- Shortness of breath
- Reduced chest expansion capability

13.4.2 Symptoms for Peritoneal Mesothelioma

- Abdominal distention
- Hernias
- Loss of appetite
- Feeling of fullness
- Abdominal swelling
- Fatigue
- Abdominal fluid buildup
- Bowel obstruction
- Weight loss for no known reason

13.4.3 Symptoms for Pericardial Mesothelioma

- Difficulty breathing
- Chest pains
- Heart palpitations
- Heart murmurs
- Fever or night sweats
- Fatigue

13.4.4 Symptoms for Testicular Mesothelioma

- Hydrocele (fluid in the scrotum)
- Swollen testicles
- Lump in scrotum
- Testicular pain

13.5 Diagnosis

Physicians detect and diagnose mesothelioma through imaging tests such as MRIs, CT scans, X-rays, and positron emission tomography (PET) scans. As discussed previously, PET scans utilize a dye containing a radioactive tracer, which shows up in higher concentrations in parts of the body where there is a high level of chemical activity, possibly indicative of the presence of disease.

In addition, biopsy of a tissue sample is checked for cancerous growth.

13.6 Methods of Treatment

The following treatment options are available for malignant mesothelioma [17–778].

13.6.1 Surgery

For patients with an early-stage mesothelioma diagnosis, doctors can remove all or most of the tumor(s) by surgery. Depending on the tumor location, surgery may include removing the mesothelial lining, one or more lymph nodes, or part or all of a lung or other organ.

13.6.2 Radiation Therapy

Utilizing targeted radiation, mesothelioma tumors can often be decreased in size, making them easier to be surgically removed. Depending on the location of the tumor, radiation is administered using an external or internal source.

13.6.3 Chemotherapy

Drugs including cisplatin, carboplatin, gemcitabine, paclitaxel, pemetrexed, raltitrexed, and vinorelbine are used alone or in combination to kill fast-growing cancer cells. Often used in conjunction with surgery, chemotherapy can destroy any remaining mesothelioma cells that the doctor was unable to remove physically.

13.6.4 Targeted Therapy

Vascular Endothelial Growth Factor (VEGF) inhibitor bevacizumab (Avastin) is used for this type of cancer.

13.6.5 Immunotherapy

Pembrolizumab (Keytruda) and nivolumab (Opdivo) as PD-1 inhibitors, and ipilimumab (Yervoy) as a CTLA-4 inhibitor are used for treating malignant mesothelioma.

13.7 Treatment Regimens

Single-agent Regimens for Systemic Therapy

Gemcitabine

1250 mg/m² IV over 30 minutes on days 1 and 8
Repeat cycle every three weeks for up to 10 cycles [46, 47].
Or 1000 mg/m² IV over 30 minutes on days 1, 8, and 15
Repeat cycle every four weeks.

Nivolumab

3 mg/kg IV over 30 minutes' infusion on day 1
Repeat cycle every 14 days [48–50].

Pemetrexed

500 mg/m² IV over 10 minutes on day 1
Repeat cycle every 21 days [51–54].
Administer folic acid 350 µg to 1000 µg orally once daily, beginning seven days before the first dose of pemetrexed. Administer vitamin B12, 1 mg intramuscularly, 1 week prior to the first dose of pemetrexed and every three cycles thereafter.
Do not substitute oral vitamin B12 for intramuscular vitamin B12.

Pembrolizumab

10 mg/kg IV over 30 minutes on day 1
Repeat cycle every three weeks [55–57].

Vinorelbine

25–30 mg/m² IV over 10 minutes on day 1
Repeat cycle every week for six weeks [58–61].

Combination Regimens**Doxorubicin + Cisplatin**

Doxorubicin: 60 mg/m² IV on day 1
Cisplatin: 60 mg/m² IV on day 1
Repeat cycle every three to four weeks [62].

Gemcitabine + Cisplatin

Gemcitabine: 1000 mg/m² IV over 30 minutes on days 1, 8, and 15
Cisplatin: 100 mg/m² IV over three hours on day 1
Repeat cycle every four weeks for six cycles [46, 47, 63].

Pemetrexed + Cisplatin

Pemetrexed: 500 mg/m² IV over 10 minutes on day 1, 30 minutes after adding cisplatin
Cisplatin: 75 mg/m² IV over two hours on day 1
Repeat cycle every 21 days for four cycles [17, 64–66].
Administer folic acid 350–1000 µg orally once daily, beginning seven days before the first dose of pemetrexed. Administer vitamin B12, 1 mg intramuscularly, one week prior to the first dose of pemetrexed and every three cycles thereafter.
Do not substitute oral vitamin B12 for intramuscular vitamin B12.

Pemetrexed + Carboplatin

Pemetrexed: 500 mg/m² IV over 10 minutes on day 1, 30 minutes after adding carboplatin
Carboplatin: AUC of 5, IV over 30 minutes on day 1
Repeat cycle every three weeks for six cycles [65, 67–70].
Administer folic acid 350–1000 µg orally once daily, beginning seven days before the first dose of pemetrexed. Administer vitamin B12, 1 mg intramuscularly, one week prior to the first dose of pemetrexed and every three cycles thereafter.
Do not substitute oral vitamin B12 for intramuscular vitamin B12.

Gemcitabine + Carboplatin

Gemcitabine: 1000 mg/m² IV over 30 minutes on days 1, 8, and 15
Carboplatin: AUC of 5, IV over 30 minutes on day 1
Repeat cycle every three weeks [71].

Gemcitabine + Vinorelbine

Gemcitabine: 1000 mg/m² IV over 30 minutes on days 1 and 8

Vinorelbine: 25 mg/m² IV over 10 minutes on days 1 and 8

Repeat cycle every 21 days [59, 72].

Gemcitabine + Pemetrexed + Gemcitabine

Gemcitabine: 1250 mg/m² IV over 30 minutes on days 1 and 8

Pemetrexed: 500 mg/m² IV over 10 minutes on day 1

Repeat cycle every 21 days [73]. Folic acid 350–1000 µg orally once daily, beginning seven days before the first dose of pemetrexed and vitamin B12 1 mg intramuscularly, 1 week prior to the first dose of pemetrexed and repeat every three cycles thereafter.

Do not substitute oral vitamin B12 for intramuscular vitamin B12.

Nivolumab + Ipilimumab

Nivolumab: 3 mg/kg IV over 30 minutes every three weeks

Ipilimumab: 1 mg/kg IV over 30 minutes every six weeks

Continue this combination treatment until disease progression, unacceptable toxicity, or up to two years in patients without disease progression [49, 74–76].

CAP

Cyclophosphamide: 500 mg/m² IV on day 1

Doxorubicin (Adriamycin): 50 mg/m² IV on day 1

Cisplatin (Platinol): 80 mg/m² IV on day 1

Repeat cycle every 21 days [77].

13.8 Possible Prevention

Because exposure to asbestos fibers (Figure 13.1) is the cause of mesothelioma, prevention of the disease consists in avoiding such contact [37, 38]. Certain occupations have a higher chance of exposure to asbestos fibers. These include firefighters, mechanics, shipyard workers, construction workers, demolition crews, boiler workers, pipefitters, steel mill workers, asbestos manufacturers, power plant workers, railroad workers, auto shop workers, miners, roofers, carpenters, floor installers, and insulation installers.

13.9 Occupational Exposure Prevention

13.9.1 Employer Responsibilities

- Air monitoring should be performed, and records kept for comparison of contaminant levels.
- Asbestos monitoring should be completed on a regular basis.
- Workers should be informed of potential asbestos hazards.
- Proper worker safety practices and controls need to be consistently enforced.

- Respiratory protection should be offered if exposure limits are exceeded.
- Workers should receive asbestos awareness training.
- Workers exposed to asbestos should receive ongoing medical surveillance.
- Protective clothes, gloves, and safety glasses should be available for employee use.

13.9.2 Employee Responsibilities

- Keep protective gear on-hand at the workplace.
- Ask the employer about any asbestos health risks in the workplace.
- Never cut, saw, drill, sand, scrape, or otherwise disturb asbestos-containing material.
- Always wear proper protective gear when work might disturb asbestos-containing material.
- Do not bring home work clothes or shoes that may be contaminated with asbestos.
- Don't sweep, dust, or vacuum asbestos debris.
- Always dispose of asbestos materials according to state and federal regulations.

13.10 Household Exposure Prevention

Some substances in homes may contain asbestos, including attic insulation, roof shingles and tar, drywall and drywall glue, floor tiles, “popcorn”-textured ceilings, joint compounds, and wrapping on pipes and electrical wires. Risk can be minimized through the following actions:

- Homebuyers should ask their home inspector or real estate agent if there is asbestos in the home.
- In older homes, do not perform do-it-yourself renovations if asbestos may be present.
- Material suspected of being asbestos should not be disturbed.
- Regularly check known asbestos products in your home for signs of wear.
- If an asbestos product is worn or has become damaged, call an abatement specialist.
- Keep residents clear of all areas that may contain asbestos.
- Never attempt to remove asbestos without help from a professional abatement specialist.

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14

Ovarian, Vaginal, and Vulvar Cancer

14.1 Introduction

Ovarian cancer affects roughly one in 75 women in the United States, according to the American Cancer Society. Ovarian cancer most commonly affects women over the age of 50, although it may occur in women of any age.

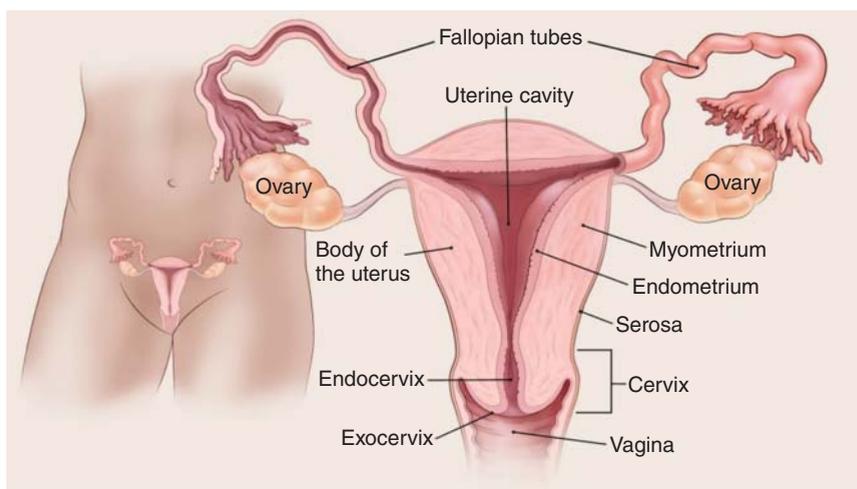


Figure 14.1 Female reproductive system, any of which can be the origin of cancer.

Ovarian cancer starts in the ovaries, which are almond-shaped female reproductive glands that generate eggs and the hormones estrogen and progesterone (Figure 14.1). Cancer may develop in the fallopian tubes (**fallopian tube cancer**) and peritoneum (**peritoneal cancer**), and both are treated similarly [1–84]. When ovarian cancer (Figure 14.2) metastasizes, it spreads to organs and tissues in the abdomen, pelvis, and lymph nodes, or to distant sites throughout the body, such as the lungs. The most common type of ovarian cancer is **epithelial**, which starts in the layer of cells that cover the ovaries and the abdominal cavity. Epithelial cancers account for almost 90% of all ovarian cancer cases.

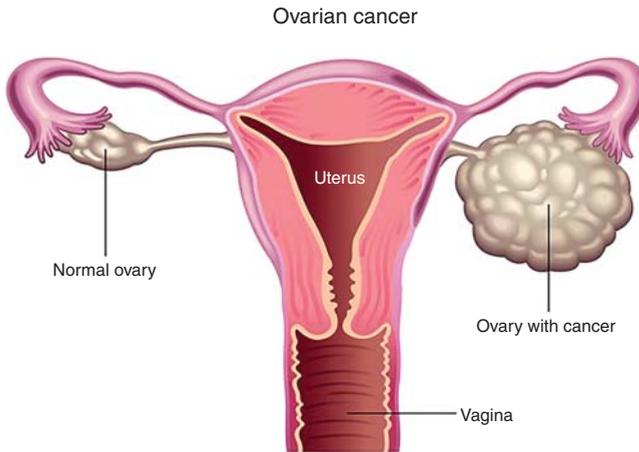


Figure 14.2 Normal ovary and ovary with cancer.

Vaginal cancer is a malignant tumor that makes tissues of the vagina. There are many different kinds of vaginal cancer. Among them, squamous cell carcinoma is the most common in women 60 and older. But it can happen at any age, even in infancy. Human papillomavirus (HPV) infection is one of the causes of vaginal cancer. If your mother took diethylstilbestrol (DES) when she was pregnant to prevent miscarriage, you may likely develop vaginal cancer.

14.2 Genes Associated with Ovarian, Vaginal, and Vulvar Cancer

Mutations most frequently associated with ovarian cancer arise in genes *NF1*, *BRCA1*, *BRCA2*, and *CDK12* [1–14]. Type I ovarian cancer, a less aggressive form, comes about due to several gene mutations, including both oncogenes such as *BRAF*, *KRAS*, *ERBB2*, *PI3CA*, and tumor suppressors such as *PTEN*. Type II cancers are more aggressive because they involve mutations in genes such as *p53*, *BRCA1*, and *BRCA2*.

Vaginal and vulvar cancer may cause the infection of HPV. It produces E6 and E7 proteins that can mutate the known tumor suppressor genes (*p53* and others) leading to uncontrolled growth of cells. If your mother took DES when she was pregnant in the 1950s to prevent miscarriages, you have a risk of developing vaginal and vulvar cancer.

14.3 Symptoms of Ovarian, Vaginal, and Vulvar Cancer

Common symptoms may include:

- Abdominal bloating, indigestion, or nausea
- Changes in appetite, such as a loss of appetite or feeling full sooner

- Pressure in the pelvis or lower back
- A more frequent or urgent need to urinate and/or constipation
- Changes in bowel movements
- Increased abdominal girth
- Tiredness or low energy
- Changes in menstruation
- Bleeding or discharge not related to menstrual periods
- A lump in the vagina
- Pain during sexual intercourse
- Pelvic pain
- Pain shortly before or after the start of a menstrual period
- Pressure, swelling, or pain in the abdomen
- A dull ache in the lower back and thighs
- Difficulty emptying bladder
- Abnormal bleeding
- Nausea or vomiting
- Pain when urinating
- Constipation
- Swelling in the legs
- Pain in the belly
- Back pain
- Itching that does not go away
- Skin changes, such as color changes or thickening
- Thickening of the skin of the vulva
- Pain or burning
- An open sore (especially if it lasts for a month or more)

14.4 Diagnosis

The detection and diagnosis of ovarian cancer are done in a variety of ways, including the physician taking a patient's **medical history** and then performing a **pelvic examination** to check for an enlarged ovary or signs of fluid in the abdomen [9–15].

Diagnostic imaging tests include an **ultrasound**, usually the first test performed if ovarian cancer is suspected; a **PET/CT**, which combines a positron emission tomography (PET) scan with a computed tomography (CT) scan; an **MRI**; and **barium enema or chest X-rays**, to see if ovarian cancer has spread to the colon or lungs, respectively.

Other tests include a **laparoscopy**, which allows doctors a view of the ovaries and other organs in the abdominal cavity through a thin, lighted tube inserted through a small incision in the lower abdomen. Blood tests are also conducted, including a **CA 125 test**, as elevated blood levels of cancer antigen 125 (CA 125) sometimes indicate the presence of ovarian cancer.

Anyone suspected of having ovarian cancer is generally referred to a specialist in female reproductive system cancers, called a *gynecologic oncologist*.

14.5 Methods of Treatment

Currently, the following treatment options are available [18–148]:

14.5.1 Surgery

A tumor on the ovary can be removed surgically.

14.5.2 Radiation Therapy

Radiation therapy is used with high-energy X-rays or particles to kill cancer cells.

14.5.3 Chemotherapy

Drugs are administered orally or intravenously, usually to block cancer cells from growing and dividing to form new cells. For ovarian cancer, albumin-bound paclitaxel (nab-paclitaxel, Abraxane), altretamine (Hexalen), capecitabine (Xeloda), cisplatin (Platinol), cyclophosphamide (Cytoxan), doxorubicin (Adriamycin), etoposide (VP-16), gemcitabine (Gemzar), ifosfamide (Ifex), irinotecan (CPT-11, Camptosar), liposomal doxorubicin (Doxil), melphalan (Alkeran), pemetrexed (Alimta), paclitaxel (Taxol), thiotepa (Tepadina), topotecan, and vinorelbine (Navelbine) are frequently the agents of choice.

14.5.4 Hormone Therapy

A combination of specialized drugs is used to lower estrogen levels in the body, which cancer cells require in order to grow. Tamoxifen as an antiestrogen can be used to treat ovarian cancer. Some aromatase inhibitors, which help for lowering estrogen levels in women after menopause including letrozole (Femara[®]), anastrozole (Arimidex[®]), and exemestane (Aromasin[®]) can be used to treat ovarian cancer.

14.5.5 Targeted Therapy

Aimed at debilitating the specific gene, protein, or tissue environment required by cancer cells for their progression, while causing minimal harm to healthy tissue, olaparib (Lynparza), rucaparib (Rubraca), and niraparib (Zejula) are three poly adenosine diphosphate-ribose polymerase (PARP) inhibitors used with ovarian cancer. Bevacizumab (Avastin) angiogenesis inhibitor, larotrectinib (Vitrakvi) and entrectinib (Rozlytrek) *NTRK* gene mutation inhibitors are targeted drugs used to treat ovarian cancer.

14.6 Drugs for Vaginal Cancer

Cisplatin, carboplatin, docetaxel, fluorouracil, irinotecan, and paclitaxel are used to treat vaginal cancer.

14.7 Drugs to Prevent Vaginal Cancer

Currently, these vaccines are available for the prevention of vaginal cancer.

- Gardasil (recombinant HPV quadrivalent vaccine)
- Gardasil 9 (recombinant HPV nonavalent vaccine)
- Recombinant HPV nonavalent vaccine
- Recombinant HPV quadrivalent vaccine

14.8 Drugs to Treat Vulvar Cancer

Bleomycin sulfate, bevacizumab, 5-fluorouracil, cisplatin, carboplatin, erlotinib, paclitaxel, pembrolizumab, and vinorelbine are used to treat this type of cancer.

14.9 Drugs to Prevent Vulvar Cancer

The following vaccines are used to prevent vulvar cancer.

- Gardasil (recombinant HPV quadrivalent vaccine)
- Gardasil 9 (recombinant HPV nonavalent vaccine)
- Recombinant HPV nonavalent vaccine
- Recombinant HPV quadrivalent vaccine

14.10 Treatment Regimens

Ovarian cancer (epithelial)

Single-agent Regimens

Altretamine

260 mg/m² orally once daily on days 1–14

Repeat cycle every two to three weeks and continue until disease progression or unacceptable toxicity prevents further therapy [124].

Bevacizumab

15 mg/kg IV over 30 minutes on day 1

Repeat cycle every 21 days [90, 148].

Capecitabine

1000 mg/m² orally twice daily on days 1–14 followed by seven days' rest period

Repeat cycle every 21 days [91].

Liposomal doxorubicin

40–50 mg/m² IV infusion over 60 minutes on day 1

Repeat cycle every 28 days [92].

Docetaxel

75 mg/m² or 100 mg/m² IV over one hour on day 1
Repeat cycle every 21 days [93].

Etoposide

50 mg/m² orally once daily on days 1–21
Repeat cycle every 28 days [94].

Gemcitabine

1000 mg/m² IV infusion over 30–60 minutes on days 1 and 8
Repeat cycle every three weeks [95].

Ixabepilone

20 mg/m² IV infusion over 60 minutes on days 1, 8, and 15
Repeat cycle every 28 days [125].

Paclitaxel

135 mg/m² IV over three hours on day 1
Repeat cycle every three weeks [126].

Nanoparticle albumin-bound paclitaxel

100 mg/m² IV over 30 minutes on days 1, 8, and 15.
Repeat cycle every 28 days [96].

Pemetrexed

500–900 mg/m² IV over 10 minutes on day 1
Repeat cycle every three weeks [97].

Topotecan

1.25–1.50 mg/m² IV over 30 minutes on Days 1–5
Repeat cycle every 21 days [98].

Vinorelbine

30 mg/m² IV over 5–10 minutes on days 1 and 8
Repeat cycle every 21 days [99].

Olaparib

300 mg orally (tablet formulation) twice daily on days 1–28
or Capsules: 400 mg orally twice daily on days 1–28
Repeat cycle every 28 days [100].

Niraparib

300 mg orally once daily on days 1–28
Repeat cycle every four weeks [49].

Rucaparib

600 mg orally twice daily on days 1–28
Repeat cycle every four weeks [101].

Cisplatin

75 mg/m² IV over 60 minutes on day 1
Repeat cycle every three weeks [102].

Carboplatin

AUC of 5, IV over 30 minutes on day 1
Repeat cycle every three weeks [103].

Doxorubicin

Doxorubicin 50 mg/m² IV over 60 minutes on day 1
Repeat cycle every 28 days [104].

Cyclophosphamide

750 mg/m² IV over 60 minutes on day 1
Repeat cycle every three weeks [105].

Ifosfamide

Mesna: 200–240 mg/m² IV over 15 minutes three times daily on days 1–5,
one dose before ifosfamide, then at four and eight hours from the
start of each ifosfamide dose
Ifosfamide: 1000–1200 mg/m² IV over three hours on days 1–5
Repeat cycle every 28 days [127].

Melphalan

3.5 mg/m² orally twice daily on days 1–5
Repeat cycle every 28 days [106].

Irinotecan

100 mg/m² IV over 90 minutes on days 1, 8, and 15
Repeat cycle every four weeks [107].

Oxaliplatin

130 mg/m² IV two hours' infusion on day 1
Repeat cycle every 21 days [108].

Pazopanib

800 mg orally once daily on days 1–28
Repeat cycle every 28 days [128].

Hormonal Therapy**Anastrozole**

Anastrozole 1 mg orally daily on days 1–28
Repeat cycle every 28 days for five years [109].

Exemestane

25 mg orally once daily

Continue until disease progression or intolerable toxicity [110].

Letrozole

2.5 mg orally once daily

Continue until disease progression or intolerable toxicity [129].

Leuprolide Acetate

3.75 mg intramuscularly once a month

Continue until disease progression or intolerable toxicity [111].

Megestrol Acetate

800 mg orally once daily for one month and then 400 mg orally once daily until tumor progression [130].

Tamoxifen

20 mg orally twice daily on days 1–28

Repeat cycle every four weeks [112].

Combination Regimens**Carboplatin + Cyclophosphamide**

Carboplatin: 300 mg/m² IV on day 1

Cyclophosphamide: 600 mg/m² IV on day 1

Repeat cycle every four weeks [131].

Cisplatin + Cyclophosphamide

Cisplatin: 75 mg/m² IV over 75 minutes on day 1

Cyclophosphamide: 750 mg/m² IV on day 1

Repeat cycle every three weeks [113].

Paclitaxel + Cisplatin

Paclitaxel: 135 mg/m² IV over 24 hours on day 1

Cisplatin: 75 mg/m² IP on day 1

Repeat cycle every three weeks [114].

Paclitaxel + Carboplatin

Paclitaxel: 175 mg/m² IV over three hours on day 1

Carboplatin: AUC of 5–6, IV over 30 minutes on day 1

Repeat cycle every three weeks [115].

Docetaxel + Carboplatin

Docetaxel: 60 mg/m² IV over one hour on day 1

Carboplatin: AUC of 6, IV over one hour on day 1

Repeat cycle every 21 days for six cycles [116].

Carboplatin + Liposomal Doxorubicin

Carboplatin: AUC of 5, IV over 30–60 minutes on day 1

Liposomal Doxorubicin: 30 mg/m² IV on day 1

Repeat cycle every four weeks [43].

Carboplatin + Ifosfamide

Carboplatin: AUC of 5, IV on day 1

Ifosfamide: 3000 mg/m² IV on day 1

Mesna: 1000 mg/m² IV on day 1

Repeat cycle every three weeks for six cycles [117].

Gemcitabine + Liposomal Doxorubicin

Gemcitabine: 1000 mg/m² IV over 30 minutes on days 1 and 8

Liposomal Doxorubicin: 30 mg/m² IV over 60 minutes on day 1

Repeat cycle every 21 days [132].

Gemcitabine + Cisplatin

Gemcitabine: 600–750 mg/m² IV over 30 minutes on days 1 and 8

Cisplatin: 30 mg/m² IV over 60 minutes on days 1 and 8

Repeat cycle every three weeks [118].

Gemcitabine + Carboplatin

Gemcitabine: 800–1000 mg/m² IV over 30 minutes on days 1 and 8

Carboplatin: AUC of 4, IV over 30 minutes on day 1

Repeat cycle every 21 days [133].

Pemetrexed + Carboplatin

Pemetrexed: 500 mg/m² IV on day 1

Carboplatin: AUC of 5, IV over 30–60 minutes on day 1

Repeat cycle every three weeks [134].

Administer folic acid 350–1000 µg orally once daily, beginning seven days before the first dose of pemetrexed. Administer vitamin B12, 1 mg intramuscularly, one week prior to the first dose of pemetrexed and every three cycles thereafter.

Do not substitute oral vitamin B12 for intramuscular vitamin B12.

Olaparib + Bevacizumab

Olaparib: 300 mg orally twice daily on days 1–21

Bevacizumab: 15 mg IV on day 1

Repeat cycle every three weeks for up to 15 months in total [119].

Carboplatin + Bevacizumab

Carboplatin: AUC of 6, IV over 60 minutes on day 1

Bevacizumab: 15 mg IV over 30–90 minutes on day 1

Repeat cycle every three weeks for six cycles.

Paclitaxel + Carboplatin + Bevacizumab

Paclitaxel: 175 mg/m² IV over three hours on day 1

Carboplatin: AUC of 6, IV over 30 minutes on day 1

Bevacizumab: 15 mg IV over 30 minutes on day 1

Repeat cycle every three weeks for six cycles [135].

VAC

Vincristine: 1.5 mg/m² (maximum 2 mg) IV on days 1, 8, 15, and 22

Actinomycin D (Dactinomycin): 300 µg/m² IV on days 1–5

Cyclophosphamide: 150 mg/m² IV over 60 minutes on days 1–5

Repeat cycle every 4 weeks [136].

VeIP

Velban (Vinblastine): 0.11 mg/kg IV over 10 minutes on days 1–2

Ifosfamide: 1200 mg/m² IV over 3 hours on days 1–5

Mesna: 240 mg/m² IV over 15 minutes three times daily, one dose before ifosfamide, then at four and eight hours from starting of each ifosfamide dose on days 1–5

Cisplatin (Platinol): 20 mg/m² IV over 60 minutes on days 1–5

Repeat cycle every three weeks [122].

JEB

Carboplatin (JM8): AUC of 6, IV over 30 minutes on day 1

Etoposide: 100 mg/m² IV over 60 minutes on days 1–5

Bleomycin: 30 units IV over 10 minutes on days 1, 8, and 15

Repeat cycle every three weeks.

VIP (Etoposide + Ifosfamide + Cisplatin)

Etoposide: 75 mg/m² IV over one hour on days 1–5

Ifosfamide: 1200 mg/m² IV over three hours on days 1–5

Mesna: 240 mg/m² IV three times daily, one dose before ifosfamide, other two doses are after four and eight hours from the start of each ifosfamide dose on days 1–5

Cisplatin: Cisplatin 20 mg/m² IV over 60 minutes on days 1–5

Repeat cycle every 21 days [123].

Cisplatin + Ifosfamide

Cisplatin: 20 mg/m² IV over 30 minutes on days 1–5

Ifosfamide: 1500 mg/m² IV on days 1–5

Mesna: 300 mg/m² IV on days 1–5, 1 hour before and 8 hours after the ifosfamide infusion for three days.

Repeat cycle every 21 days for eight cycles [137].

Paclitaxel + Ifosfamide

Paclitaxel: 135 mg/m² IV over three hours on day 1
 Ifosfamide: 1600 mg/m² IV over three hours on days 1–3
 Mesna: 320 mg/m² IV over 15 minutes three times daily on days 1–3
 Filgrastim: 5 µg/kg/d starts on day 4 until the granulocyte count ≥ 2000/m²
 Repeat cycle every 21 days for eight cycles [138].

Oxaliplatin + Capecitabine

Oxaliplatin: 130 mg/m² IV over two hours on day 1
 Capecitabine: 850 mg/m² orally twice daily on days 1–14
 Repeat cycle every 21 days for six cycles [139].

Oxaliplatin + Capecitabine + Bevacizumab

Oxaliplatin: 130 mg/m² IV over two hours on day 1
 Capecitabine: 850 mg/m² orally twice daily on days 1–14
 Bevacizumab: 15 mg IV over 30–90 minutes on day 1
 Repeat cycle every three weeks for six cycles [139]. Then bevacizumab maintenance is 15 mg/kg on day 1, repeat cycle every three weeks for 12 cycles.

Gemcitabine + Carboplatin + Bevacizumab

Gemcitabine: 1000 mg/m² IV over 30 minutes on days 1 and 8
 Carboplatin: AUC of 4, IV over 30 minutes on day 1
 Bevacizumab: 15 mg/kg IV on day 1
 Repeat cycle every 21 days [144]. Then bevacizumab maintenance dose is 15 mg/kg on day 1, repeat cycle every 21 days.

Topotecan + Sorafenib

Topotecan: 1.25 mg/m² IV over 30 minutes on days 1–5
 Sorafenib: 400 mg orally twice daily on days 6–15
 Repeat cycle every 21 days for six cycles [147]. The daily maintenance sorafenib is 400 mg orally for one year.

14.10.1 Treatment Regimens for Germ Cell Ovarian Cancer**BEP**

B = Bleomycin

E = Etoposide phosphate

P = Platinol (cisplatin)

Bleomycin: 30 units IV over 10 minutes on days 1, 8, and 15

Etoposide: 100 mg/m² IV over 60 minutes on days 1–5

Cisplatin: 20 mg/m² IV over 60 minutes on days 1–5

Repeat cycle every 21 days for three to four cycles [120, 121].

14.11 Risk Factors/Possible Preventions

- **Age:** Two-thirds of women diagnosed with ovarian cancer are aged 55 or older [60–72].
- **Family history:** Women with a mother, sister, grandmother, or aunt who has had ovarian cancer have a higher risk of developing this cancer.
- **Genetic mutations:** Some women who develop ovarian cancer have an inherited mutation on one of two genes called breast cancer gene 1 (*BRCA1*) and breast cancer gene 2 (*BRCA2*). Women with the *BRCA1* mutation have a 35–70 percent higher risk of developing ovarian cancer [68]. Women with the *BRCA2* mutation have a 10–30 percent higher risk. However, the vast majority of women who are diagnosed with ovarian cancer do not have either mutation. Nonetheless, those women concerned about this risk factor might consider getting tested for these specific mutations through a gynecologic oncologist.
- **Lynch syndrome or Peutz-Jeghers syndrome:** Women who have these inherited genetic disorders have a higher risk of developing ovarian cancer. Lynch syndrome is characterized by a higher risk of cancers of the digestive tract, gynecologic tract, and other organs. Peutz-Jeghers syndrome indicates an increased risk of developing polyps in the digestive tract and several other types of cancer, including in the breast, colon, rectum, pancreas, stomach, testicles, ovaries, lungs, and cervix.
- **Prior medical history:** Women previously diagnosed with breast, colorectal, or endometrial cancer have a higher risk of developing ovarian cancer.

Factors that may *lower* the risk of ovarian cancer include:

- **Childbearing status:** Women who have delivered at least one child, especially before age 30, are at a lower risk for this type of cancer. The more children a woman has, the less risk she has for developing ovarian cancer. Women who breastfeed further reduce their risk.
- **Birth control:** Women who have used oral contraceptives for at least three months are at a lower risk for ovarian cancer. The risk is lower the longer the contraceptives are taken, and the decreased risk continues for many years after contraceptives are stopped.
- **Gynecologic surgery:** A tubal ligation (tying the fallopian tubes) or hysterectomy (removing the uterus but not the ovaries) reduces the risk of developing ovarian cancer.

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15

Pancreatic Cancer

15.1 Introduction

The pancreas is an organ in the abdomen which sits in front of the spine above the level of the belly button. It has two main functions, one as part of the *endocrine system*, releasing hormones into the bloodstream or bodily tissue and the other as part of the *exocrine system*, which operates by secreting chemicals into ducts that lead to their target organs. The pancreas produces *insulin*, a hormone that controls blood sugar levels (endocrine function), and manufactures and secretes digestive enzymes, which help break down dietary proteins, fats, and carbohydrates, into the intestine (exocrine function). The dietary enzymes produced by the pancreas include trypsin and chymotrypsin for protein digestion, amylase for carbohydrate digestion, and lipase for fat breakdown.

Pancreatic cancer occurs when cells in the pancreas start to multiply out of control and form a mass [1–61]. Like other cancers, these malignant cells can metastasize to other parts of the body (Figure 15.1). There are a number of types of pancreatic cancer, with the most common being **adenocarcinomas**, which account for about 85% of cases. According to the National Cancer Institute, approximately 55 440 new cases of pancreatic cancer were diagnosed in the United States in 2018, with 44 330 people dying from the disease. Currently, pancreatic cancer is the eighth most common cancer for females and the fourth leading cause of cancer mortality in both males and females. Tobacco smoking or use, obesity, diabetes, and certain rare genetic mutations are the major risk factors for pancreatic cancer [1–7, 10].

15.2 Genes Associated with Pancreatic Cancer

Like other cancers, pancreatic cancer can be caused by gene changes (mutations) that turn on oncogenes or turn off tumor suppressor genes. Ninety percent of pancreatic cancer cases have a mutation in the *KRAS* gene. In higher and more harmful

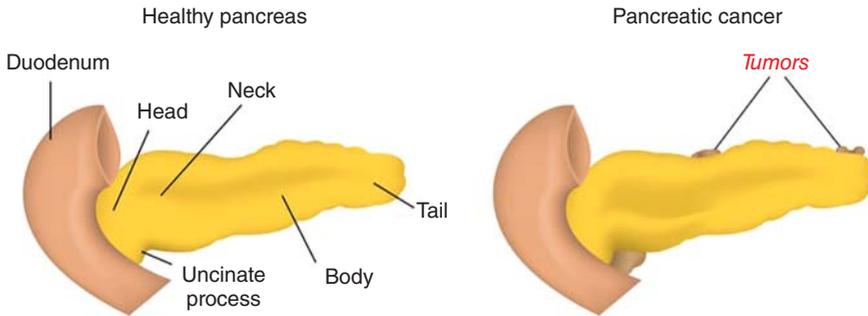


Figure 15.1 Pancreatic cancer.

grades of the disease, other genes linked to the disease include *CDKN2A* (which codes for several proteins, including *p16*, *TP53*, *BRAF*, and *SMAD4*).

15.3 Symptoms of Pancreatic Cancer

Unfortunately, the symptoms of pancreatic cancer generally do not appear until the cancer is in an advanced state. Signs may include:

- Pain in the upper abdomen which radiates to the back
- Loss of appetite
- Unintended weight loss
- Depression
- New-onset diabetes
- Blood clots
- Fatigue
- Yellowing of skin and eyes (jaundice)
- Vomiting
- Itchy skin
- Nausea
- Enlarged gallbladder
- Digestive problems (pale and/or greasy stools)
- Dark or irregularly colored urine

15.4 Diagnosis

Pancreatic cancer is detected and diagnosed through CT scans, tissue biopsy, liver function testing, and various blood tests [14, 15].

15.5 Methods of Treatment

Current therapeutic options for the management of pancreatic cancer are as follows [22–96]:

15.5.1 Surgery

Cancerous tumors are surgically removed from the pancreas.

15.5.2 Radiation Therapy

High-energy X-rays or other particle sources are directed at tumors in order to destroy the cancer cells [17].

15.5.3 Chemotherapy

Drugs designed to curtail the growth and progression of cancer cells are administered. In the case of pancreatic cancer, chemotherapy agents used include gemcitabine (Gemzar), 5-fluorouracil (5-FU), oxaliplatin (Eloxatin), albumin-bound paclitaxel (Abraxane), capecitabine (Xeloda), cisplatin (Platinol), irinotecan (Camptosar), mitomycin, and among others [22–31, 33, 34, 38–46].

15.5.4 Targeted Therapy

Specialized medicines target the specific genes involved with cancer's growth and survival while leaving healthy cells relatively unharmed. Erlotinib is a targeted drug sometimes used in advanced pancreatic cancer cases [25]. Its effect is to block a protein on cancer cells called epidermal growth factor receptor (EGFR), which normally helps the cells proliferate. Olaparib (Lynparza) as a poly adenosine diphosphate-ribose polymerase (PARP) inhibitor, larotrectinib (Vitrakvi) and entrectinib (Rozlytrek) as neurotrophic tyrosine receptor kinase (NTRK) inhibitors can be used for certain pancreatic cancer [32]. Everolimus (Afinitor) as an mTOR inhibitor and sunitinib malate (Sutent) as a multi-targeted receptor tyrosine kinase (RTK) inhibitor are used.

15.5.5 Immunotherapy

As discussed in earlier chapters, immunotherapy is also called biologic therapy, and it works by supporting the body's natural defense mechanisms against cancer invasion. The therapy involves administering chemicals either produced by the body or manufactured in a laboratory to bolster patients' immune response. Currently, medicines referred to as checkpoint inhibitors are being tried on pancreatic cancer cases. Immunological checkpoints are molecules on certain cells, both normal and cancerous, that need to be activated – or inactivated – to initiate an immune response. Pembrolizumab (Keytruda) is an immune checkpoint inhibitor (a monoclonal antibody), which interferes with the binding of PD-1 to L1 proteins present on cancer cells that basically communicate to the body not to attack them.

15.5.6 Drugs for Gastroenteropancreatic Neuroendocrine Tumors

Everolimus (Afinitor Disperz), lanreotide acetate (Somatuline Depot), and lutetium lu 177-dotatate (Lutathera) are used to treat this type of cancer.

15.6 Treatment Regimens for Pancreatic Cancer

Adjuvant Therapy

Single-agent Regimens

5-Fluorouracil + Leucovorin

5-fluorouracil: 425 mg/m² IV on days
1–5

Leucovorin: 20 mg/m² IV on days
1–5

Repeat cycle every four weeks for six cycles [66].

Gemcitabine

1000 mg/m² IV over 30 minutes on days 1, 8, and 15

Repeat cycle every four weeks for six cycles [67].

Combination Regimens

Gemcitabine + Capecitabine

Gemcitabine: 1000 mg/m² IV on days 1, 8, and 15

Capecitabine: 880 mg/m² orally twice daily on days 1–21

Repeat cycle every four weeks for a total of six cycles [66].

FOLFIRINOX

Fol = Folinic acid (Leucovorin calcium)

F = 5-fluorouracil

IRIN = Irinotecan hydrochloride

OX = Oxaliplatin

Folinic acid (Leucovorin): 400 mg/m² IV over two hours on day 1

Irinotecan: 150 mg/m² IV over 90 minutes on day 1

Oxaliplatin: 85 mg/m² IV over two hours on day 1

5-fluorouracil: 2400 mg/m² continuous infusion over 46 hours on
days 1 and 2

Repeat cycle every two weeks for up to 12 cycles [68].

Systemic Therapy for Locally Advanced/Recurrent/Metastatic Disease

Single-agent Regimens

Capecitabine

800–1,250 mg/m² orally twice daily on days 1–14

Repeat cycle every three weeks with two weeks on and one week off for two to six cycles [69].

Gemcitabine

1000 mg/m² IV over 30 minutes on days 1, 8, and 15

Repeat cycle every four weeks (three weeks on and one week off) [70].

Olaparib

300 mg orally twice daily.

Continue until disease progression or unacceptable toxicity [32].

5-fluorouracil

5-fluorouracil: 425 mg/m² IV on days 1–5

Leucovorin: 20 mg/m² IV on days 1–5

Repeat cycle every four weeks for six cycles [66].

Entrectinib (NTRK gene fusion-positive)

600 mg orally once daily on days 1–28

Repeat cycle every 28 days [83].

Larotrectinib (NTRK gene fusion-positive)

100 mg orally twice daily

Continue until disease progression or the occurrence of an unacceptable level of adverse events [84, 95].

Pembrolizumab

200 mg IV once every three weeks

Continue for two years or until disease progression, unacceptable toxicity, or patient withdrawal [85, 96].

Combination Regimens**Capecitabine + Gemcitabine**

Capecitabine: 830 mg/m² orally twice daily on days 1–14

Gemcitabine: 1000 mg/m² IV over 30 minutes on days 1, 8, and 15

Repeat cycle every four weeks (three weeks on/one week off) [71].

Capecitabine + Erlotinib

Capecitabine: 1000 mg/m² orally twice daily on days 1–14

Erlotinib: 150 mg orally once daily on days 1–21

Repeat cycle every three weeks [93].

Gemcitabine + Erlotinib

Gemcitabine: 1000 mg/m² IV over 30 minutes once per week for seven weeks, then one week rest

Erlotinib: 100 mg orally once daily on days 1–56

Repeat cycle every eight weeks [72].

Gemcitabine + Oxaliplatin

Gemcitabine: 1000 mg/m² IV over 100 minutes on day 1

Oxaliplatin: 100 mg/m² IV over two hours on day 2

Repeat cycle every 14 days [94].

Gemcitabine + Albumin-bound Paclitaxel

Albumin-bound paclitaxel: 125 mg/m² IV over 30 minutes on days 1, 8, and 15

Gemcitabine: 1000 mg/m² IV over 30 minutes on days 1, 8, and 15

Repeat cycle every four weeks for two to six cycles [73].

Liposomal Irinotecan + Leucovorin + 5-Fluorouracil

Liposomal irinotecan: 80 mg/m² IV on day 1 (equivalent to 70 mg/m² of the irinotecan-free base)

Leucovorin: 400 mg/m² IV on day 1

5-fluorouracil: 2,400 mg/m² IV continuous infusion over 46 hours on days 1 and 2

Repeat cycle every two weeks [74, 75].

FOLFIRINOX

Oxaliplatin: 85 mg/m² IV over two hours on day 1

Folinic acid (leucovorin): 400 mg/m² IV over two hours on day 1, followed by

Irinotecan: 135 mg/m² IV over 90 minutes on day 1

5-fluorouracil: 300 mg/m² IV bolus on day 1, followed by

5-fluorouracil: 2400 mg/m² IV continuous infusion over 46 hours on days 1 and 2

Repeat cycle every two weeks [68].

Gemcitabine + Cisplatin

Gemcitabine: 750 mg/m² IV over 30 minutes on day 1

Cisplatin: 30 mg/m² IV over 60 minutes on day 1

Repeat cycle every 14 days for six cycles [76, 77].

15.7 Risk Factors and Possible Preventions

Factors that may increase the risk of pancreatic cancer include [47–52]:

- **Age:** Most pancreatic cancer patients are aged 65 years and older
- **Chronic inflammation** of the pancreas (pancreatitis)
- **Diabetes**

- **Family history of genetic syndromes** that can increase cancer risk, including a *BRCA2* gene mutation, Lynch syndrome, and familial atypical mole-malignant melanoma (FAMMM) syndrome
- **Family history of pancreatic cancer**
- **Smoking**
- **Obesity**

Prevention strategies include not smoking, or quitting if already a smoker; maintaining a healthy weight while adhering to a diet rich in fruit, colorful vegetables, and whole grains; and avoiding red meat (cow, goat, and pig), opting instead for chicken or fish.

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16

Prostate Cancer

16.1 Introduction

The prostate is a walnut-sized gland situated behind the base of a male's penis, in front of the rectum and below the bladder. The prostate produces part of the seminal fluid, which is the liquid in semen that protects, supports, and helps transport sperm.

As men get older, the prostate can become larger, sometimes resulting in blockage of the urethra in a condition called benign prostatic hypertrophy (BPH). BPH is a condition associated with growing older, and it can cause symptoms similar to those of prostate cancer. Although, BPH has not been associated with a greater risk of having prostate cancer.

Prostate cancer starts when healthy cells in the prostate change and grow out of control, making a tumor [1–105]. Tumors can be cancerous or benign. Malignant prostate cancer can grow and spread to other parts of the body (Figure 16.1). A benign tumor can grow but will not spread to other parts of the body.

Prostate cancer is not very common in comparison to other types of cancer because many prostate tumors do not spread so quickly to other parts of the body. In fact, most prostate cancers grow so slowly that they may not cause symptoms or problems for years, or, possibly, ever. If prostate cancer cannot be well-regulated with current treatments, it may cause symptoms such as pain and fatigue, ultimately leading to death. Treatment decisions are based on evaluating the pattern of cancer growth in each individual patient.

16.2 Genes Associated with Prostate Cancer

The gene mutations responsible for prostate cancer are usually acquired mutations versus hereditary [4–21]. For some hereditary prostate cancer cases, mutations in tumor suppressor genes *BRCA1*, *BRCA2*, and *HOXB13* have been associated with the development of prostate and other types of cancers [9, 11, 12, 17, 21, 23]. Also, men with *BRCA2* or *HOXB13* mutations appear to be at higher risk of experiencing the more aggressive, life-threatening forms of prostate cancer. Other gene mutations include *CHEK2*, *ATM*, *PALB2*, *RAD51D*, *MSH2*, *MSH6*, *MLH1*, *PMS2*, and many more also responsible for prostate cancer.

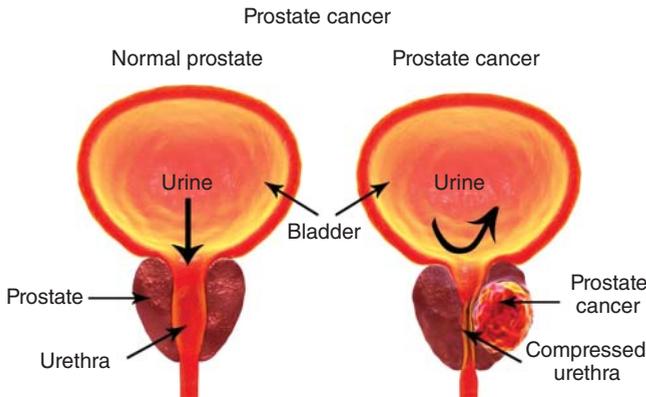


Figure 16.1 Depiction of prostate cancer.

16.3 Symptoms of Prostate Cancer

- More frequent urination
- Weak urine flow
- The need to strain to empty the bladder
- The urge to urinate more frequently at night
- Difficulty starting (hesitancy)
- Blood in the urine
- Blood in the seminal fluid
- Dribbling of urine
- New onset of erectile dysfunction
- Painful ejaculation
- Burning sensation during urination
- Discomfort or pain when sitting

If cancer has spread outside the prostate gland, the following may also be experienced:

- Pain in the back, hips, thighs, shoulders, or other bones
- Swelling or fluid buildup in the legs or feet
- Weight loss
- Tiredness
- Change in bowel movements

16.4 Diagnosis

There is no standard form of screening for prostate cancer and testing options are still being studied to find those that will provide the most information and least risk [25–31]. One procedure is a digital rectal examination done via the rectum by a physician or nurse, who feels for lumps or any abnormality on the prostate. A blood test can also be done to check for levels of prostate-specific antigen (PSA), which may

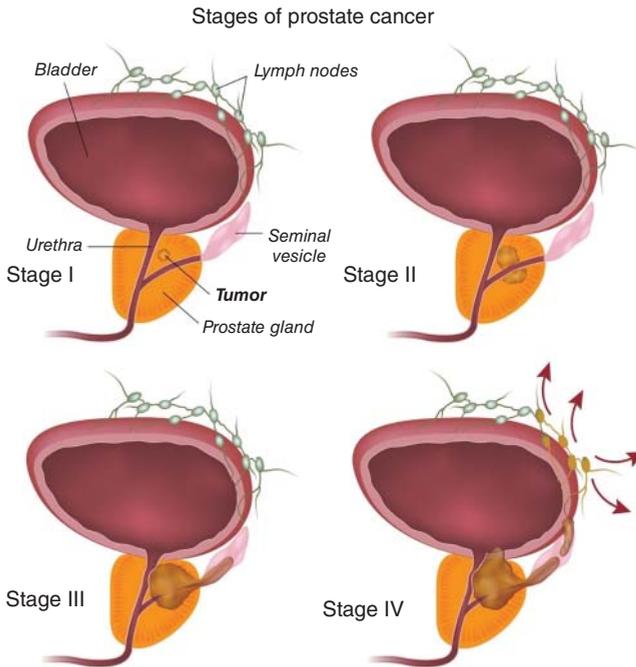


Figure 16.2 Stages of prostate cancer development.

be elevated if prostate cancer is present. However, BPH or other non-cancer prostate problems can also result in high PSA levels. Abnormal symptoms or test results are further explored through ultrasound, MRI, or a biopsy. Like other cancers, prostate cancer can be categorized into four stages depending on spreading (Figure 16.2).

16.5 Methods of Treatment

The following treatment options are available for prostate cancer [32–122]:

16.5.1 Surgery

A prostate tumor and some surrounding healthy tissues are removed surgically.

16.5.2 Radiation Therapy

As previously discussed, high-energy X-rays or other particle sources are directed at tumors in order to destroy the cancer cells.

16.5.3 Cryotherapy

Cryotherapy (also called cryosurgery or cryoablation) uses a very cold temperature to freeze and kill prostate cancer cells.

16.5.4 Chemotherapy

For prostate cancer, chemotherapy often begins with administering docetaxel (Docefrez, Taxotere) combined with a steroid called prednisone (multiple brand names). Mitoxantrone (Novantrone), estramustine (Emcyt), and cabazitaxel (Jevtana) can be used after docetaxel stops working.

16.5.5 Targeted Therapy

Rucaparib (Rubraca) and olaparib (Lynparza) are PARP inhibitors that can be used to treat prostate cancer.

16.5.6 Immunotherapy

Sipuleucel-T (Provenge) is a cancer vaccine that boosts the immune system to help it attack prostate cancer cells. Pembrolizumab (Keytruda) is a PD-1 inhibitor that can be used to treat this type of cancer.

16.5.7 Hormone Therapy

Orchiectomy (surgical castration) is a type of hormone therapy where the surgeon can remove the testicles where testosterone and dihydrotestosterone (DHT) are made. Luteinizing hormone-releasing hormone (LHRH) agonists include leuprolide (Lupron and Eligard), goserelin (Zoladex), triptorelin (Trelstar), and histrelin (Vantas) are used to reduce testosterone levels. LHRH antagonists including degarelix (Firmagon) and relugolix (Orgovyx) can be used to reduce testosterone levels. Abiraterone (Zytiga) and ketoconazole (Nizoral) can be used to lower androgen levels. Antiandrogens medicines include flutamide (Eulexin), bicalutamide (Casodex), nilutamide (Nilandron), enzalutamide (Xtandi), apalutamide (Erleada), and darolutamide (Nubeqa), which are used to stop androgens from working.

16.6 Treatment Regimens

Single-agent Regimens

Goserelin

3.6 mg subcutaneous (SC) implant on day 1

Repeat cycle every four weeks.

Or

10.8 mg subcutaneous implant on day 1

Repeat cycle every 12 weeks [84].

Histrelin

50-mg SC implant on day 1

Repeat cycle every one year [85].

Apalutamide

240 mg orally once daily

Continue until disease-free or adverse events, or withdrawal of consent from patients [75].

Bicalutamide

50 mg orally once daily

Continue until disease progression or intolerable toxicity [86, 87].

Aminoglutethimide

250 mg orally twice daily or 500 mg orally twice daily if tolerated

Continue until disease progression or intolerable toxicity [106].

Darolutamide

600 mg orally twice daily

Continue until disease progression or intolerable toxicity [72].

Enzalutamide

160 mg orally once daily

Continue until disease progression or intolerable toxicity [74, 88, 89].

Degarelix

120 mg SC × two doses (two separate injections totaling 240 mg) starting dose, then after 28 days, the monthly maintenance dose is 80 mg SC

Repeat maintenance dose every four weeks [90].

Docetaxel

75 mg/m² IV on day 1

Repeat cycle every three weeks [91].

Estramustine

14 mg/kg orally daily in three to four divided doses every six to eight hours

Continue until disease progression or unacceptable toxicity [107].

Flutamide

250 mg orally three times per day

Repeat cycle every four weeks [86].

Leuprolide

7.5 mg SC or IM monthly or 22.5 mg IM every three months or 30 mg IM every four months or 50 mg intravenously (IV) every six months [122].

Nilutamide

300 mg orally once daily on days 1–30, followed by:

150 mg orally once daily [92].

Prednisone

5 mg orally twice daily

Repeat cycle every 21 days [93–95].

Olaparib

300 mg orally twice daily on days 1–28
Repeat cycle every four weeks [96].

Rucaparib

600 mg orally twice daily on days 1–28
Repeat cycle every 28 days [97].

Triptorelin

3.75 mg IM monthly or 11.25 mg IM every three months or 22.5 mg IM every six months [92].

Paclitaxel

135–170 mg/m² IV over 24 hours' continuous infusion on day 1
Repeat cycle every three weeks for six cycles [108].

Sipuleucel-T

Supply as an infusion bag, IV over 60 minutes on day 1
Repeat cycle every 14 days for three cycles [43].

Relugolix

360 mg orally loading dose on day 1, then 120 mg orally once daily from day 2
Continue until disease progression or unacceptable toxicity [84].

Combination Regimens**Abiraterone + Prednisone**

Abiraterone: 1000 mg orally once daily on days 1–28
Prednisone: 5 mg orally twice daily on days 1–28
Repeat cycle every four weeks and continue for two years or until disease progression [98, 99].

Cabizataxel + Prednisone

Cabizataxel: 25 mg/m² IV over 60 minutes on day 1
Prednisone: 10 mg orally once daily on days 1–21
Repeat cycle every 21 days [100, 101]

Docetaxel + Prednisone

Docetaxel: 75 mg/m² IV over 60 minutes on day 1
Prednisone: 5 mg orally twice daily on days 1–21
Repeat cycle every 21 days [91].

Mitoxantrone + Prednisone

Mitoxantrone: 12 mg/m² IV over 30 minutes on day 1
Prednisone: 5 mg orally twice daily on days 1–21
Repeat cycle every three weeks [93].

Estramustine + Etoposide

Estramustine: 15 mg/kg orally daily in four divided doses on days 1–21

Etoposide: 50 mg/m² orally daily in two divided doses on days 1–21

Repeat cycle every four weeks (three weeks on/one week off) [109].

Estramustine + Vinblastine

Estramustine: 600 mg/kg orally once daily on days 1–42

Vinblastine: 4 mg/m² IV once per week for six weeks

Repeat cycle every eight weeks (two weeks' rest, then continue) [110].

Paclitaxel + Estramustine

Estramustine: 600 mg/kg orally daily

Paclitaxel: 120 mg/m² IV continuous infusion on days 1–4 (96 hours)

Repeat cycle every 21 days [111].

Docetaxel + Estramustine

Estramustine: 420 mg orally for the first four doses and 280 mg orally for the next five doses on days 1–3 for two weeks

Docetaxel: 35 mg/m² IV over 30 minutes on day 2 of weeks 1 and 2

Repeat cycle every three weeks (two weeks on and one week off) [112].

Docetaxel + Leuprolide

Docetaxel: 75 mg/m² IV on day 1 for every 28 days

Leuprolide: 7.5 mg IM on day 1 for every 21 days

Continue until disease progression or unacceptable toxicity [113].

Flutamide + Goserelin

Flutamide: 250 mg orally three times daily on days 1–28

Goserelin: 10.8 mg SC every three months

Repeat cycle every three months [114].

Flutamide + Leuprolide

Flutamide: 200 mg orally three times daily on days 1–28

Leuprolide: 7.5 mg IM on day 1

Repeat cycle every four weeks [115].

Docetaxel + Prednisone + Bevacizumab

Docetaxel: 75 mg/m² IV over one hour on day 1

Prednisone: 5 mg orally twice daily on days 1–21

Bevacizumab: 15 mg/kg IV on day 1

Repeat cycle every three weeks [116].

Abiraterone + Methylprednisolone

Abiraterone: 500 mg orally once daily on days 1–28

Methylprednisolone: 4 mg orally twice daily on days 1–28

Repeat cycle every 28 days [76, 77, 98, 99].

Etoposide + Carboplatin

Etoposide 100 mg/m² IV over 60 minutes on days 1–3

Carboplatin: Area under the curve (AUC) of 5–6, IV over 30 minutes on day 1

Repeat cycle every three to four weeks for four to six cycles [103, 117, 118].

Etoposide + Cisplatin

Etoposide: 80–100 mg/m² IV over 60 minutes on days 1–3

Cisplatin: 75–80 mg/m² IV over 60 minutes on day 1

Repeat cycle every three weeks for four to six cycles [102, 118, 119].

Docetaxel + Carboplatin

Docetaxel: 60–75 mg/m² IV over 60 minutes on day 1, given first

Carboplatin: AUC of 4–6, IV over 30 minutes on day 1, given second

Repeat cycle every three weeks for four to six cycles [118, 120, 121].

16.7 Risk Factors/Possible Preventions

The following factors may be related to developing prostate cancer [44–54]:

Family history. Prostate cancer that runs in a family, called familial prostate cancer, occurs in approximately 5–10% of cases. This type of prostate cancer develops because of a combination of shared genes and shared environmental or lifestyle factors. The risk of developing this type of cancer is greater if:

- Three or more first-degree relatives have a history of prostate cancer
- Prostate cancer is present in three generations on the same side of the family
- Two or more close relatives, such as a father, brother, son, grandfather, uncle, or nephew, on the same side of the family, were diagnosed with prostate cancer before the age of 55.

Diet and exercise. Regularly eating foods high in fat, especially animal fat, may increase the risk of developing prostate cancer risk. Research regarding the effect of diet is ongoing. It is suggested, however, that:

- Dairy product consumption should be reduced.
- Consume more plant-derived fats than animal fats.
- Fatty fish such as salmon, tuna, and herring should be added to the diet in order to supply the body with omega-3 fatty acids, which have been linked to a reduced risk of prostate cancer.
- Eating a diet high in vegetables, fruits, and legumes, such as beans and peas, may decrease the risk of prostate cancer.

Moreover, it is recommended that maintenance of a healthy weight and participation in regular exercise are effective behaviors to lower the risk of prostate and other forms of cancer.

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17

Stomach (Gastric) Cancer

17.1 Introduction

The stomach is a bean-shaped, muscular sack located behind the lower ribs, which can expand to temporarily store food. Once food reaches the stomach, sphincter muscles close off the top opening of the stomach, as well as the point of exit to the small intestine. The stomach muscles churn the food physically, and the stomach lining secretes hydrochloric acids and enzymes to aid in its chemical digestion. The lower stomach sphincter then opens in a regulated way to allow partially digested food to move into the small intestine, where further digestion and absorption take place.

17.2 Genes Associated with Stomach Cancer

Stomach cancer, also known as gastric cancer, occurs when the genetic material of cells in the stomach acquires mutations that lead to abnormal growth and reproduction (Figure 17.1). The buildup of excess cells forms a tumor in some part of the stomach [1–65]. According to the World Health Organization (WHO), stomach cancer is the sixth most common type of cancer worldwide, with 1.03 million cases diagnosed in 2018.

The most common identified risk factor for developing stomach cancer is infection by the bacterium *Helicobacter pylori*, which plays a role in more than 60% of cases [1–14]. Other factors include smoking (tobacco use), obesity, drinking alcohol, and consumption of pickled vegetables. Approximately, 10% of cases run in families, and between 1% and 3% of cases are due to genetic syndromes inherited from a parent, as is the case in hereditary diffuse gastric cancer (*CDH1* gene mutation). Furthermore, the inherited mutated gene causing hereditary diffuse gastric cancer also heightens the risk for lobular breast cancer. *Foxp-3* polymorphism (rs3761548) activates T cells (Tregs) that might contribute to the development of stomach cancer.

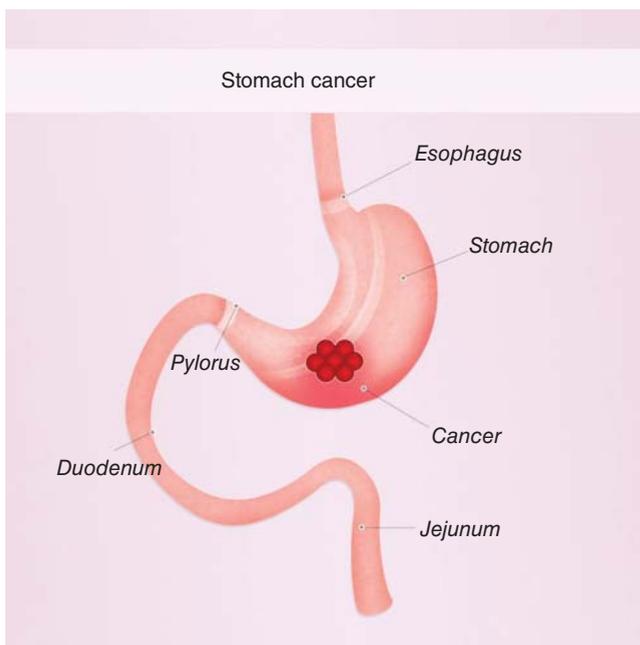


Figure 17.1 Depiction of stomach cancer.

17.3 Symptoms of Stomach Cancer

Early-to-mid-stage stomach cancer can cause the following symptoms:

- Sensation of extreme fullness during meals
- Swallowing difficulties (dysphagia)
- Feeling bloated after meals
- Frequent burping or trapped wind
- Heartburn
- Persistent indigestion
- Stomachache or pain in the breastbone
- Vomiting, which may contain blood

In people at increased risk for stomach cancer, the following symptoms should be regarded as *urgent*:

- Dysphagia
- Indigestion combined with
 - unexpected weight loss
 - vomiting
 - anemia
- Fatigue
- Breathlessness

In general, those aged 55 years and over who experience persistent indigestion should consult their physician. In addition, individuals who develop indigestion and have at least one of the following in their medical history should also see a doctor:

- A close relative who has/had stomach cancer
- Barrett's esophagus – Also known as BE or Barrett's syndrome, this is a medical condition characterized by changes in the lining of the lower esophagus, which make it more similar to the lining of the small intestine rather than the esophagus.
- Dysplasia (an abnormal collection of typically precancerous cells)
- Gastritis (inflammation of the lining of the stomach)
- Pernicious anemia: This is a condition in which the stomach is unable to properly absorb vitamin B12 from food.
- A history of stomach ulcers

With advanced-stage stomach cancer, the following symptoms become more apparent:

- Fluid buildups in the stomach
- Anemia
- Black stools that contain blood
- Fatigue
- Loss of appetite
- Weight loss

17.4 Stages of Stomach Cancer

Stomach cancer progresses through defined stages (Figure 17.2). With increased stage, the condition is more advanced and chances of survival lessen.

Stage 0: Highly abnormal precancerous cells are present in the mucosa (mucous membrane) but have not spread to other layers of the stomach or nearby lymph nodes.

Stage IA: Cancer has moved into one of the next layers of the stomach lining, such as the submucosa, but not to nearby lymph nodes.

Stage IB: Cancer has progressed into one of the next layers of the stomach lining and into one or two nearby lymph nodes.

Stage IIA: Cancer has developed into an even deeper layer, and may have spread to one or two lymph nodes. If the tumor has grown deep enough, it may not need to have spread to lymph nodes in order to qualify as stage IIA cancer.

Stage IIB: The tumor may not have necessarily spread as deep as a stage IIA stomach cancer, but has spread to a greater number of lymph nodes, sometimes up to 15.

Stage IIIA: This stage is characterized by cancer that has spread to a deeper layer of the lining of the stomach and up to 15 lymph nodes; or, it has started to grow through the stomach wall and spread to fewer lymph nodes. In addition, it has begun to reach nearby organs and structures.

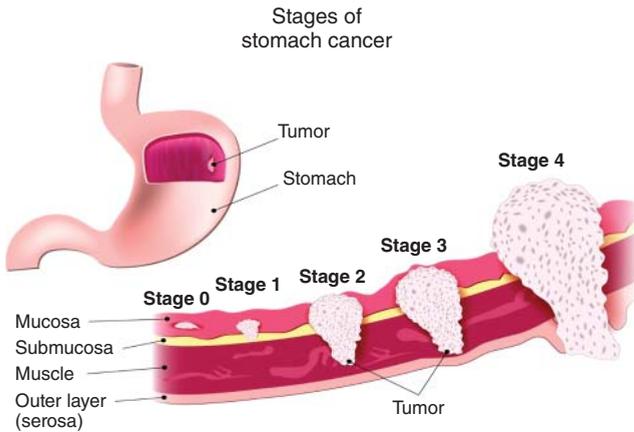


Figure 17.2 Classification of malignant stomach cancer by clinical stage.

Stage IIIB: Cancer has not grown as deep as stage IIIA stomach cancer, but has spread to over 16 lymph nodes. It has started to reach nearby organs and structures.

Stage IIIC: Cancer has either grown through most of the stomach layers and spread to over 16 lymph nodes, or it has spread to nearby organs and structures and up to 15 lymph nodes.

Stage IV: Cancer has spread to distant sites, although it may not have spread to nearby lymph nodes.

17.5 Diagnosis

Diagnosis of stomach cancer begins with a **physical exam**, including reporting of the patient's **complete medical history**. If warranted, other tests are conducted, including blood chemistry studies. A **complete blood count (CBC)** is performed, in which a sample of the patient's blood is checked for the number of red blood cells, as well as the portion of the sample made up of red blood cells only, white blood cells, and platelets. In addition, the sample is analyzed for the amount of hemoglobin, the protein found in red blood cells that binds oxygen.

Imaging procedures such as a **CT scan** or **PET scan** provide physicians with detailed pictures of the stomach and other parts of the digestive tract. Not as frequently nowadays, a **barium X-ray** or **barium swallow** might be conducted. As discussed earlier, in this procedure, the patient drinks a chalky liquid, which contains barium, allowing a detailed image of the stomach to show up on an X-ray.

An **upper endoscopy** may be done, which involves the insertion of a long, thin, flexible tube with a video camera at the end called an endoscope, into the stomach via the esophagus. In this way, a doctor can check for any abnormalities or signs of cancer. If the doctor sees tissue that appears abnormal, a sample can be taken for biopsy, or analysis to check for the presence of cancer cells.

A **laparoscopy** may be required if the physician suspects that stomach cancer has spread, especially to the lining of the abdominal cavity called the *peritoneum*.

As discussed in a previous chapter, laparoscopy is a procedure conducted while the patient is under general anesthesia, and involves the insertion of a thin viewing tube with a camera into the stomach, in this case, through a small incision in the lower part of this organ.

17.6 Methods of Treatment

The following is a list of treatment methods for stomach (gastric) cancer [15–98]:

17.6.1 Surgery

Depending on the stage of cancer, various types of surgery are performed:

- Early-stage cancer confined to the uppermost lining of the stomach can be removed via a procedure called an **endoscopic mucosal resection**. Small tumors are taken with specialized instrumentation inserted in the same manner as during diagnostic endoscopy.
- **Subtotal gastrectomy** involves surgical removal of part of the stomach.
- **Total gastrectomy** is the surgical removal of the entire stomach.

If the tumor is blocking the stomach, but cancer cannot be completely removed by standard surgery, the following procedures may be used:

17.6.2 Endoluminal Stent Placement

In this procedure, a thin, expandable tube called a *stent* is inserted to keep a passage (in this case, the esophagus) open. When tumors are blocking the proper passage of food into or out of the stomach, a stent may be placed in the opening to the stomach from the esophagus, or at the exit of the stomach to the small intestine, in order to allow the patient to eat normally.

17.6.3 Endoluminal Laser Therapy

An endoscope with a laser attached is inserted into the body. A laser is an intense beam of light that can be used as a knife to cut through and destroy/remove tumors.

17.6.4 Gastrojejunostomy

The jejunum is part of the small intestine approximately midway between its beginning near the stomach and ending point, where it connects to the large intestine. In this surgery, the stomach is connected to the jejunum to basically bypass a tumor blocking the normal exit from the stomach into the small intestine. This allows food and medicine to pass from the stomach into the small intestine.

17.7 Radiation Therapy

Regarding the treatment of cancer, high-energy radiation is sometimes used to target and destroy tumor cells. In the case of stomach cancer, however, typical radiation therapy is not commonly employed due to the risk of damaging nearby organs and tissue. The use of radiation to shrink tumors before surgery, called *neoadjuvant radiation*, and after surgery to kill remaining cancer cells, called *adjuvant radiation*, vary according to each patient's particular gastric cancer scenario.

17.8 Chemotherapy

Specialized cytotoxic medicines are administered to patients to stop cancerous cells from replicating and growing. Medications travel in the bloodstream and are thus able to reach and destroy cancer cells at their origin as well as in other areas to which they may have metastasized. The agents chosen depend upon the type of cancer and the drugs' potential damage to healthy cells. 5-FU (fluorouracil), capecitabine, carboplatin, cisplatin, docetaxel, epirubicin, irinotecan, mitomycin, oxaliplatin, paclitaxel, rifluridine, and tipiracil are used to treat stomach cancer.

17.9 Targeted Medications

Sunitinib (Sutent) and imatinib (Gleevec) are two medications that attack specific types of abnormalities in cancerous cells for people with gastrointestinal stromal tumors. For stage IV gastric cancer or gastric cancer that has recurred, monoclonal antibodies, such as trastuzumab (Herceptin) or ramucirumab (Cyramza), might be tried. Trastuzumab inhibits the effect of the growth factor protein HER2 and ramucirumab inhibits the protein vascular endothelial growth factor (VEGF) and may prevent the development of new blood vessels that tumors need to grow. Larotrectinib (Vitrakvi) and entrectinib (Rozlytrek) inhibit tyrosine receptor kinase (TRK) proteins that can be used to treat stomach cancer with *NTRK* gene mutation. Fam-trastuzumab deruxtecan (Enhertu) is a monoclonal antibody linked to an antibody-drug conjugate (ADC) that can be used to treat advanced HER2-positive stomach cancer.

17.10 Immunotherapy

Nivolumab (Opdivo) and pembrolizumab (Keytruda) target PD-1 protein and can be used to boost the immune response against cancer cells.

17.11 Treatment Regimens for Stomach Cancer

These regimens are provided as references to the latest treatment strategies and educational purposes only [55–111]. Oncologists must choose and verify treatment options based on the individual patient's physical condition.

Preoperative Chemoradiotherapy Regimens

Oxaliplatin: 85 mg/m² IV on day 1

Leucovorin: 400 mg/m² IV on day 1

5-fluorouracil: 400 mg/m² IV loading dose then 800 mg/m² IV continuous infusion daily on days 1 and 2

Repeat cycle every two weeks for three cycles with radiation [99].

Oxaliplatin + Capecitabine

Oxaliplatin: 85 mg/m² IV on days 1, 15, and 29 for three doses

Capecitabine: 625 mg/m² orally twice daily on days 1–5 weekly for five weeks with 50.4 Gy radiation [98].

Cisplatin + 5-Fluorouracil

Cisplatin: 75–100 mg/m² IV on days 1 and 29

5-fluorouracil: 750–1000 mg/m²/day IV continuous infusion on days 1–4 and 29–32
Single 35 days' cycle with radiation [56].

Cisplatin + Capecitabine

Cisplatin: 30 mg/m² IV on day 1

Capecitabine: 800 mg/m² orally twice daily on days 1–5

Repeat cycle every seven days for five cycles with radiation [100]

Paclitaxel + 5-Fluorouracil

Paclitaxel: 45–50 mg/m² IV 30 minutes on day 1

5-fluorouracil: 300 mg/m² IV continuous infusion on days 1–5

Repeat cycle weekly for five cycles with radiation [101].

Paclitaxel + Carboplatin

Paclitaxel: 50 mg/m² IV 30 minutes on day 1

Carboplatin: AUC of 2, IV over 30 minutes on day 1

Repeat cycle every week for five cycles with radiation [102].

Perioperative Chemoradiotherapy Regimens**FLOT**

Oxaliplatin: 85 mg/m² IV on day 1

Docetaxel (Taxotere): 50 mg/m² IV on day 1

Leucovorin: 200 mg/m² IV on day 1

5-fluorouracil: 2600 mg/m² IV continuous infusion over 24 hours on day 1

Repeat cycle every two weeks for four cycles with radiation [66, 67]. This regimen is given for four preoperative cycles and then four postoperative cycles.

Oxaliplatin + Leucovorin + 5-Fluorouracil

Oxaliplatin: 85 mg/m² IV on day 1

Leucovorin: 200 mg/m² IV on day 1

5-fluorouracil: 2600 mg/m² IV continuous infusion over 24 hours on day 1

Repeat cycle every 14 days with radiation [66].

Cisplatin + 5-Fluorouracil

Cisplatin: 50 mg/m² IV on day 1

5-fluorouracil: 2000 mg/m² IV continuous infusion over 48 hours on days 1 and 2

Repeat cycle every 14 days with radiation [66].

Capecitabine + Oxaliplatin

Oxaliplatin: 130 mg/m² IV on day 1

Capecitabine: 1000 mg/m² orally twice daily on days 1–14

Repeat cycle every 21 days [66].

5-Fluorouracil + Leucovorin

5-fluorouracil: 425 mg/m² IV on days 1–5

Leucovorin: 20 mg/m² IV on days 1–5

After four weeks, radiation is started and 5-fluorouracil and leucovorin are repeated [68, 69].

Epirubicin + Cisplatin + 5-Fluorouracil

Epirubicin: 50 mg/m² IV on day 1

Cisplatin: 60 mg/m² IV on day 1

5-fluorouracil: 200 mg/m²/day IV continuous infusion over 24 hours on days 1–21

Repeat cycle every three weeks for three preoperative and three postoperative cycles [17]

Postoperative Chemoradiotherapy Regimens**Oxaliplatin + Leucovorin + 5-Fluorouracil**

Oxaliplatin: 85 mg/m² IV on day 1

Leucovorin: 400 mg/m² IV on day 1

5-fluorouracil: 400 mg/m² IV loading dose, then 1200 mg/m² IV continuous infusion daily on days 1 and 2

Repeat cycle every 14 days with radiation [64].

Oxaliplatin + Capecitabine

Oxaliplatin: 130 mg/m² IV on day 1

Capecitabine: 1000 mg/m² orally twice daily on days 1–14

Repeat cycle every three weeks with radiation [103].

Nivolumab

240 mg IV over 30 minutes on day 1

Repeat cycle every two weeks for 16 weeks, followed by 480 mg over 30 minutes every four weeks from week 17 [104].

Capecitabine

750–1000 mg/m² orally twice daily on days 1–14

Repeat cycle every four weeks with radiation (two weeks on and two weeks off) [97].

Leucovorin + 5-Fluorouracil

Leucovorin: 400 mg/m² IV on days 1, 2, 15, and 16

5-fluorouracil: 400 mg/m² IV loading dose and then 1200 mg/m² IV 24 hours' continuous infusion on day 1

Repeat cycle every four weeks with radiation [69].

Systemic Therapy Regimens for Unresectable/Locally Advanced/Recurrent/Metastatic Disease Stage**Single-agent Regimens****5-Fluorouracil**

500 mg/m² IV on days 1–5

Repeat cycle every four weeks [71].

Docetaxel

75–100 mg/m² IV over 60 minutes on day 1

Repeat cycle every three weeks [72–74].

Or 35 mg/m² IV over 30 minutes on day 1

Repeat cycle weekly [72–74].

Irinotecan

250–350 mg/m² IV on day 1

Repeat cycle every three weeks [75, 76].

Or 125 mg/m² IV weekly [76].

Paclitaxel

120–250 mg/m² IV infusion over 3 hours on day 1

Repeat cycle every three weeks [74, 77].

Or 80 mg/m² IV infusion over 60 minutes weekly

Repeat cycle every four weeks [77].

Pembrolizumab

200 mg IV infusion over 30 minutes on day 1

Repeat cycle every three weeks [78].

Ramucirumab

8 mg/kg IV on day 1

Repeat cycle every two weeks [79].

TAS-102

35 mg/m² orally twice daily on days 1–5 and 8–12

Repeat cycle every four weeks [80].

5-Fluorouracil + Leucovorin

Leucovorin: 200 mg/m² IV on days 1–5, given first

5-fluorouracil: 370 mg/m² IV on days 1–5, given second

Repeat cycle every three weeks [81].

Capecitabine

750–1000 mg/m² orally twice daily on days 1–14

Repeat cycle every 28 days; one cycle before and two cycles after chemoradiation [97].

Entrectinib (for *NTRK* gene fusion-positive tumors)

600 mg orally once daily

Continue until disease progression or intolerable toxicity occurs [105].

Larotrectinib (for *NTRK* gene fusion-positive tumors)

100 mg orally twice daily

Continue until disease progression or unacceptable toxicity [106].

Trastuzumab

8 mg/kg IV loading dose on day 1 of cycle 1, then 6 mg/kg IV at the beginning of cycle 2

Repeat cycle every 21 days [107].

Trastuzumab Deruxtecan

6.4 mg/kg IV every three weeks

Continue until disease progression or intolerable toxicity [80].

Combination Regimens**Cisplatin + 5-Fluorouracil**

Cisplatin: 100 mg/m² IV on day 1

5-fluorouracil: 1000 mg/m²/day IV continuous infusion on days 1–5

Repeat cycle every four weeks [82, 109].

Capecitabine + Cisplatin

Cisplatin: 80 mg/m² IV infusion over 2 hours on day 1

Capecitabine: 1000 mg/m² orally twice daily on days 1–14

Repeat cycle every three weeks [83].

Paclitaxel + Cisplatin

Paclitaxel: 135–200 mg/m² IV over 24 hours' infusion on day 1

Cisplatin: 75 mg/m² IV on day 2 with granulocyte colony-stimulating factor support

Repeat cycle every three weeks [84, 85].

Docetaxel + Cisplatin

Docetaxel: 70–85 mg/m² IV infusion over 60 minutes on day 1

Cisplatin: 70–75 mg/m² IV infusion over 60 minutes on day 1

Repeat cycle every three weeks [86, 87].

Irinotecan + Cisplatin

Irinotecan: 65 mg/m² IV on days 1 and 8

Cisplatin: 25 mg/m² IV on days 1 and 8

Repeat cycle every three weeks (two weeks on and one week off) [88].

Paclitaxel + Ramucirumab

Paclitaxel: 80 mg/m² IV on days 1, 8, and 15

Ramucirumab: 8 mg/kg IV on days 1 and 15

Repeat cycle every four weeks [89].

Paclitaxel + Carboplatin

Paclitaxel: 200 mg/m² IV over 3 hours' infusion on day 1, followed by carboplatin: AUC of 5, IV over 30 minutes on day 1

Repeat cycle every 21 days [90].

Docetaxel + Irinotecan

Docetaxel: 35 mg/m² IV infusion over 1 hour on days 1 and 8

Irinotecan: 50 mg/m² IV infusion over 30 minutes on days 1 and 8

Repeat cycle every 21 days [111].

DCF

Docetaxel: 75 mg/m² IV on day 1

Cisplatin: 75 mg/m² IV on day 1

5-fluorouracil: 750 mg/m²/day IV continuous infusion over 24 hours daily on days 1–5

Repeat cycle every three weeks [91].

ECF

Epirubicin: 50 mg/m² IV bolus on day 1

Cisplatin: 60 mg/m² IV on day 1

5-fluorouracil: 200 mg/m²/day IV continuous infusion over 24 hours daily on days 1–21

Repeat cycle every three weeks [92].

ECX

Epirubicin: 50 mg/m² IV bolus on day 1

Cisplatin: 60 mg/m² IV on day 1

Capecitabine (Xeloda): 625 mg/m² orally twice daily on days 1–21

Repeat cycle every three weeks [92, 93].

EOF

Epirubicin: 50 mg/m² IV bolus on day 1

Oxaliplatin: 130 mg/m² IV infusion over 2 hours on day 1

5-fluorouracil: 200 mg/m² IV continuous infusion over 24 hours daily on days 1–21

Repeat cycle every three weeks [92, 93].

EOX

Epirubicin: 50 mg/m² IV bolus on day 1

Oxaliplatin: 130 mg/m² IV infusion over 2 hours on day 1

Capecitabine (Xeloda): 625 mg/m² orally twice daily on days 1–21

Repeat cycle every 21 days [92, 93].

FLO

Oxaliplatin: 85 mg/m² IV over 2 hours' infusion on day 1

Leucovorin: 200 mg/m² IV over 2 hours' infusion on day 1

5-fluorouracil: 2600 mg/m² IV continuous infusion over 24 hours on day 1

Repeat cycle every two weeks [94].

FOLFOX

Oxaliplatin: 85 mg/m² IV infusion over 2 hours on day 1

Leucovorin: 400 mg/m² IV over 2 hours' infusion on day 1

5-fluorouracil: 400 mg/m² IV bolus on day 1 followed by 2400 mg/m² IV continuous infusion over 46 hours on days 1–3

Repeat cycle every two weeks [95].

Capecitabine + Cisplatin + Trastuzumab

Capecitabine (Xeloda): 1000 mg/m² orally twice daily on days 1–14

Cisplatin: 80 mg/m² IV on day 1

Trastuzumab: 8 mg/kg IV loading dose (cycle 1 only), then 6 mg/kg IV every three weeks

Repeat cycle every three weeks [96].

5-Fluorouracil + Cisplatin + Trastuzumab

Cisplatin: 80 mg/m² IV on day 1

Trastuzumab: 8 mg/kg IV loading dose, then 6 mg/kg IV every three weeks.

5-fluorouracil: 800 mg/m² IV continuous infusion on days 1–5

Repeat cycle every three weeks [96].

Oxaliplatin + Capecitabine

Oxaliplatin: 85 mg/m² IV on days 1, 15, and 29

Capecitabine: 625 mg/m² orally twice daily on days 1–5

Repeat cycle every five weeks [98].

Margetuximab + Pembrolizumab

Margetuximab: 15 mg/kg IV on day 1

Pembrolizumab: 200 mg IV on day 1

Repeat cycle every 21 days [108].

Regorafenib + Nivolumab

Regorafenib: 80 mg once daily on days 1–21

Nivolumab: 3 mg/kg every two weeks

Repeat cycle every four weeks [109].

17.12 Risk Factors

The following is a list of factors associated with a heightened risk of developing stomach (gastric) cancer [33–41]:

17.12.1 Certain Medical Conditions

People suffering from esophagitis, gastroesophageal reflux disease (GERD), peptic stomach ulcers, Barrett's esophagus, chronic gastritis, and stomach polyps are at higher risk for stomach cancer.

17.12.2 Smoking

Regular, long-term smokers are twice as likely to develop stomach cancer as non-smokers.

17.12.3 Helicobacter Pylori Infection

Although harmless for most people, this bacterium can cause infection and stomach ulcers in some. Having chronic ulcers places an individual at higher risk for gastric cancer.

17.12.4 Family History

Those with a close relative who has had stomach cancer may be more likely to develop the same disease.

17.12.5 Foods Containing Aflatoxins

Aflatoxins are a family of toxins made by a certain fungus sometimes present on agricultural products. These cancer-associated toxins are sometimes found in crude vegetable oils, corn, cocoa beans, tree nuts, peanuts, figs, and other dried foods and spices.

17.12.6 Diet

People who regularly eat salted fish, salty foods, smoked meats, and pickled vegetables have a higher risk of developing gastric cancer.

17.12.7 Age

Stomach cancer is most often found in individuals 55 years of age and older.

17.12.8 Gender

Males are twice as likely to be diagnosed with stomach cancer as females.

17.12.9 Previous or Existing Cancers

Individuals with a history of esophageal cancer or non-Hodgkin's lymphoma are at higher risk of developing stomach cancer. In addition, males who have or have had prostate, bladder, or testicular cancer are at greater risk, as are females with a history of cervical, ovarian, or breast cancer.

17.12.10 Some Surgical Procedures

Having stomach surgery or surgery in another area that affects the stomach, such as the vagus nerve, may increase that individual's risk of stomach cancer.

17.13 Possible Preventions

The exact cause of gastric cancer is still being studied. As such, prevention guidelines are somewhat generalized and serve as preventatives against most types of cancer:

- Eat plenty of fruit and vegetables.
- Reduce or eliminate salty and smoked foods from the diet.
- Stop smoking and do not start.

- Discuss medical history with a physician to see if any prior conditions might increase the risk of stomach cancer.

Tips for maintaining gastrointestinal health include:

- Eat small meals at a time.
- Avoid carbonated drinks.
- Eat a diet rich in fruits and vegetables, and decrease consumption of fatty foods and red meat.
- Quit smoking and do not start.
- Maintain healthy body weight.
- Engage in moderate activity after a meal, for a couple of hours.
- Avoid eating shortly before bedtime.
- Avoid hard-to-digest foods that result in stomach upset.
- Drink at least eight glasses of water or other non-caffeinated liquid per day.
- Use acid-neutralizing medications, if needed.
- Take in at least 30 grams of fiber daily to maintain healthy bowel movements.
- Exercise 40 to 60 minutes, three to five times a week to help with total gastrointestinal health. This might include walking, running, weight training, or resistance training.
- Consider taking a probiotic supplement to help balance the microbiome in the digestive tract.
- Go to the bathroom when you have the urge. Do not wait.
- For hard stools, try over-the-counter stool softeners or a tablespoon of mineral oil, olive oil, or flaxseed oil.

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18

Thyroid Cancer

18.1 Introduction

The thyroid gland is a small, likely butterfly-shaped organ located in the throat. It has a variety of essential roles in the body's maintenance and well-being. Part of the endocrine system, the thyroid controls metabolism through its production of the hormones calcitonin, T4 (thyroxine or tetraiodothyronine), and T3 (tri-iodothyronine), which it releases into the bloodstream. These hormones regulate the rate at which cells and organs turn nutrients into energy and the amount of oxygen cells used, and furthermore control a variety of major bodily functions, from maintenance of body temperature to heart function and brain development.

18.2 Genes Associated with Thyroid Cancer

Thyroid cancer occurs when cells genetically mutate or change on *RET*, *BRAF*, *MEN*, *CDKN1B*, and other genes [1–11]. The abnormal cells start multiplying in the thyroid gland and eventually form a tumor (Figure 18.1). If detected early, thyroid cancer is one of the most curable types of cancer [12–36].

18.3 Types of Thyroid Cancer

Scientists have identified four main forms of thyroid cancers:

18.3.1 Papillary Thyroid Cancer

Comprising up to 80% of all thyroid cancer cases, this form grows slowly, but it can spread to the lymph nodes of the neck.

18.3.2 Follicular Thyroid Cancer

Approximately, 15% of all thyroid cancers are of this type, which can progress into lymph nodes with the possibility of metastasizing via the blood vessels.

Thyroid cancer

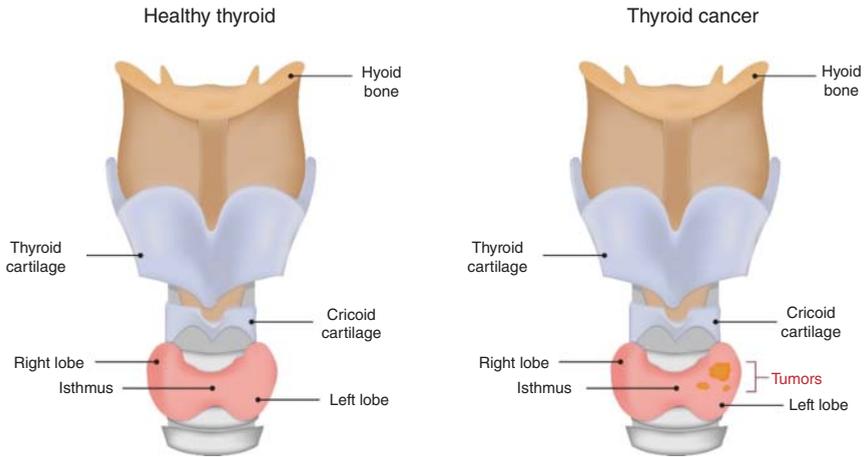


Figure 18.1 Healthy thyroid versus cancerous thyroid.

18.3.3 Medullary Cancer

This form is likely hereditary in origin, with the specific gene mutations conveyed between family members. It constitutes approximately 5% of all thyroid cancer cases.

18.3.4 Anaplastic Thyroid Cancer

Although the rarest form of the disease, this type is the most aggressive.

18.4 Thyroid Cancer Symptoms

- Neck pain, throat pain
- Swollen lymph nodes or enlarged thyroid gland
- Lump in the neck
- Difficulty swallowing
- Vocal changes, hoarseness
- Cough



18.5 Diagnosis

Any lumps detected on the neck should be reported to a physician immediately [12–14]. The chances are great that it is not cancer, but early detection is a key factor in the successful treatment of this and other types of cancer.

- **Physical Exam.** Physicians feel for any lumps or nodules on the neck.
- **Genetic Tests.** Based on a patient’s family history, doctors may perform genetic testing to find out if the patient has any genes known to predispose them to thyroid cancer.
- **Biopsy.** A sample of the suspicious tissue is extracted and analyzed for the presence of cancer cells.
- **Ultrasound.** Using high-frequency sound waves to create an image of the thyroid, doctors can detect any nodules forming on this organ.
- **CT Scan.** Computed tomography makes use of X-rays to provide a picture of internal bodily structures. Through this screening, physicians can see the size and location of thyroid cancer, and determine whether it has spread to other parts of the body.
- **PET Scan.** Positron emission tomography involves the use of small amounts of radioactive material, called *radiotracers*, along with a special camera, and computer-assisted imagery to get a more detailed image of organs and tissue. Because a PET scan can detect changes at the cellular level, it can potentially enable a very early-stage diagnosis of cancer.

18.6 Staging of Thyroid Cancer

The “TNM” Staging System – created by the American Joint Committee on Cancer, this system of classifying the degrees of thyroid cancer progression focuses on three characteristics:

T: Tumor. How big is it, and has it spread to other areas of the body?

N: Nodes. Has the thyroid cancer spread to nearby lymph nodes?

M: Metastasis. Has thyroid cancer spread to other organs or areas of the body, namely the lungs, liver, or bones?

18.6.1 Papillary or Follicular Thyroid Cancer Patients under the Age of 45

- **Stage I:** The tumor can be any size. It may have spread to nearby tissues or nearby lymph nodes, but it has not spread to more distant parts of the body.
- **Stage II:** The tumor is any size, and it may have spread to the lymph nodes. It has also spread to other parts of the body, such as the lungs or bones.

18.6.2 Papillary or Follicular Thyroid Cancer Patient Aged 45 Years and Older

- **Stage I:** Cancer is in the thyroid only, and tumor size is 2 centimeters (cm) or smaller.

- **Stage II:** Cancer is in the thyroid only, and tumor size is more than 2 cm but less than 4 cm.
- **Stage III:** The tumor is larger than 4 cm and has spread to tissues near the thyroid, or the tumor is small and has progressed to nearby lymph nodes.

Papillary and Follicular Thyroid Cancer, Stage IV

Stage IV disease indicates cancer has spread beyond the thyroid. Letters are assigned to correspond to the extent of progression.

- **Stage IVA:** Cancer has spread beyond the thyroid to beneath the skin or to the larynx, esophagus, or trachea. Also classified as Stage IVA is the formation of a smaller tumor in a more distant lymph node.
- **Stage IVB:** The tumor has grown toward your spine or into nearby large blood vessels, including the carotid arteries, which transport blood to the brain, face, and neck. Cancer might also have spread to the lymph nodes.
- **Stage IVC:** Cancer has progressed beyond the thyroid to distant sites of the body, possibly affecting lungs, bones, and lymph nodes.

18.6.3 Medullary Thyroid Cancer

The following stages are assigned, irrespective of a patient's age.

- **Stage I:** The tumor is 2 cm or smaller in diameter, and confined to the thyroid.
- **Stage II:** The tumor is larger than 2 cm, although still confined to the thyroid. Alternatively, the tumor is any size but has spread to tissues beyond the thyroid; however, cancer has not yet affected the lymph nodes.
- **Stage III:** The tumor may be any size and may also have spread to tissue beyond the thyroid. Also, cancer may have spread to the lymph nodes near the voice box and windpipe.
- **Stage IV:** As previously described for follicular and papillary thyroid cancer, stage IV medullary thyroid cancer means that cancer has spread to distant sites of the body, and the letters "A," "B," and "C" are assigned to show where.

18.6.4 Anaplastic Thyroid Cancer

This is a fast-growing type of thyroid cancer, and as such, it is further classified only as stage IVA, IVB, or IVC. By the time it is discovered, this cancer may already have spread throughout the neck.

- **Stage IVA:** The primary cancerous tumor is contained in the thyroid, and it may or may not have spread to nearby lymph nodes.
- **Stage IVB:** The tumor has spread outside the thyroid, and may or may not have progressed to nearby lymph nodes.
- **Stage IVC:** Cancer has spread to other areas of the body such as the lungs and bones. It may also have invaded distal lymph nodes.

18.7 Methods of Treatment

The following are current therapeutic options [15–69]:

18.7.1 Surgery

Surgery to extract a tumor in the thyroid, called thyroidectomy, is the most widely used treatment method for thyroid cancer.

18.7.2 Radioactive Iodine Ablation

The thyroid gland, as well as most thyroid tumors, absorb iodine. Radioactive iodine ablation involves administering special radioactive iodine to be absorbed by the thyroid cancer cells, which are then killed by the radioactive substances in it [17–20, 27, 28].

18.7.3 External Beam Radiation

Also known as X-ray therapy, this treatment involves the use of radiation to destroy cancer cells. Very carefully administered doses of radiation are given over several weeks, with the aim of protecting healthy surrounding tissues as much as possible.

18.7.4 Thyroid Hormone Therapy

For thyroid cancer patients who had their entire thyroid surgically removed, the hormones produced by this gland need to be replaced artificially through medication. Thyroid hormone pills are prescribed, with the added benefit that they help keep any leftover cancer cells from returning and progressing. This is achieved through the medication's effect of lowering blood levels of thyroid-stimulating hormone (TSH), which is naturally manufactured by the pituitary gland. TSH normally activates the thyroid to make thyroid hormones, but it also encourages the growth of cancer.

18.7.5 Chemotherapy

Carboplatin, cyclophosphamide, dacarbazine, docetaxel, doxorubicin, 5-fluorouracil, paclitaxel, streptozocin, and vincristine are used for thyroid cancer treatment [20, 21].

18.7.6 Targeted Therapy

More recently, targeted medications have been developed that affect specific parts of cancer cells, to slow or stop the cells' growth. Normally taken in pill form, these

agents generally have fewer side effects than standard chemotherapy. Current targeted therapy drugs for thyroid cancer are vandetanib (Caprelsa), sorafenib (Nexavar), lenvatinib (Lenvima), carbozantinib (Cometriq), selpercatinib (Retevmo), larotrectinib (Vitrakvi), entrectinib (Rozlytrek), pralsetinib (Gavreto), dabrafenib (Tafinlar), trametinib (Mekinist), and others [19, 20, 22–25, 31, 35, 40, 41, 43, 45].

18.8 Treatment Regimens

Single-Agent Regimens

Axitinib

5–10 mg orally twice daily
Repeat cycle every four weeks [68].

Cabozantinib (for Medullary Thyroid Cancer)

140 mg orally once daily in a fasting state (two hours before and one hour after administration of cabozantinib)
Continue until disease progression or unacceptable toxicity [61].

Dabrafenib (BRAF-positive)

150 mg orally twice daily on days 1–28
Repeat cycle every four weeks [24].

Doxorubicin

60 mg/m² IV once every three weeks or 20 mg/m² IV once weekly
Repeat cycle every three weeks [61, 62].

Entrectinib (patients with NTRK gene fusion-positive tumors)

600 mg orally once daily on days 1–28
Repeat cycle every four weeks [25].

Larotrectinib (patients with NTRK gene fusion-positive tumors)

100 mg twice daily on days 1–28
Repeat cycle every four weeks [23, 43, 68].

Lenvatinib

24 mg orally once daily with or without food
Repeat every 28 days and continue until disease progression or unacceptable toxicity [22].

Pazopanib

800 mg orally once daily
Repeat cycle every four weeks and continue until disease progression, drug intolerance, or both occur [47].

Pralsetinib (RET fusion positive)

400 mg orally once daily on an empty stomach
Continue until disease progression or intolerable toxicity [63].

Selpercatinib (RET fusion positive)

120 mg orally twice daily (weight <50 kg)

160 mg orally twice daily (weight >50 kg)

Continue until disease progression or unacceptable toxicity [64].

Sorafenib

400 mg orally twice daily

Continue until disease progression or unacceptable toxicity [53].

Sunitinib

50 mg orally once daily for four weeks

Repeat cycle every six weeks [65].

Vandetanib (for Medullary Thyroid Cancer)

300 mg orally once daily

Continue until disease progression or unacceptable toxicity [50].

Paclitaxel

60–90 mg/m² IV on day 1

Repeat cycle weekly [69].

Pembrolizumab

200 mg IV on day 1

Repeat cycle every 21 days [69].

Combination Regimens**Cisplatin + Doxorubicin**

Cisplatin: 40 mg/m² IV on day 1

Doxorubicin: 60 mg/m² IV on day 1

Repeat cycle every three weeks [62].

Docetaxel + Doxorubicin

Docetaxel: 20 mg/m² IV on day 1

Doxorubicin: 20 mg/m² IV on day 1

Repeat cycle weekly [69].

Paclitaxel + Carboplatin

Paclitaxel: 50 mg/m² IV over one hour on day 1

Carboplatin: AUC 2 IV over 30 minutes on day 1

Repeat cycle weekly for six weeks with concurrent radiation [69].

Dabrafenib + Trametinib (patients with BRAF V600E mutation positive)

Dabrafenib: 150 mg orally twice daily on days 1–28

Trametinib: 2 mg orally once daily on days 1–28

Repeat cycle every four weeks [24].

18.9 Possible Preventions

Most people who develop thyroid cancer have no known risk factors for the disease. Early detection and intervention are the greatest factors in successfully eliminating this disease [38–42].

Thyroid cancer has been linked to low iodine levels in the diet and to head/neck radiation exposure, especially during childhood. In the United States, iodine is added to salt and some breads. This supplementation helps reduce the risk of thyroid disorders, including thyroid cancer.

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19

Endometrial Cancer

19.1 Introduction

Endometrial cancer is the most commonly diagnosed gynecologic cancer. This cancer is the most common form of uterine cancer. So, it is frequently referred to as uterine cancer. This cancer affects the female reproductive organs, the uterus, the hollow, pear-shaped organ, where a baby grows. Endometrial cancer (Figure 19.1) begins when cells in the endometrium (the inner lining of the uterus) grow out of control [1–50]. There are two types of uterine cancers: endometrial cancer (common) and uterine sarcoma (rare). Endometrial cancer may often be cured but uterine sarcoma is more aggressive and difficult to treat. If untreated, endometrial cancer can spread to the bladder or rectum, or it can spread to the vagina, fallopian tubes, ovaries, and more distant organs. This cancer grows slowly; with regular medical checkups, it is usually found before spreading from the uterus to other parts of the body.

19.2 Genes Associated with Endometrial Cancer

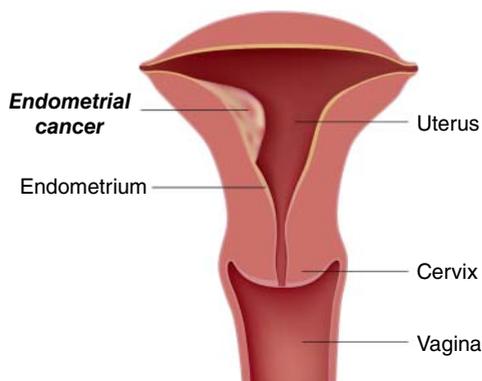
Mutations of tumor suppressor genes and oncogenes such as *ARID1A*, *CTNNB1*, *FGFR2*, *KRAS*, *PIK3R1*, *P53*, *PTEN*, *MLH1*, *RASSF1A*, *SPRY2*, *PPP2R1A*, *CDH1*, *CDKN2A*, *PIK3CA*, *STK15*, *CCNE1*, *ERBB2*, and *CCND1* may cause for development of endometrial cancer [2–5, 13]. Mutations in *BRCA1* or *BRCA2* genes also predispose females to endometrial cancer, and in cases where these mutations are evidenced, a transvaginal ultrasound is utilized to obtain an image of females' ovaries and/or uterus.

19.3 Symptoms

- (a) Bleeding or discharge not related to your periods (menstruation) – over 90 percent of women diagnosed with endometrial cancer have abnormal vaginal bleeding
- (b) Postmenopausal bleeding
- (c) Difficult or painful urination

Endometrial cancer

Figure 19.1 Endometrial cancer.



- (d) Pain during intercourse
- (e) Pain and/or mass in the pelvic area
- (f) Vaginal discharge that may range from pink and watery to thick, brown, and foul-smelling
- (g) An enlarged uterus, detectable during a pelvic exam
- (h) Unexpected weight loss
- (i) Weakness and pain in the lower abdomen, back, or legs. This occurs when cancer has spread to other organs of the body.

19.4 Endometrial Cancer Diagnosis

Diagnosis of endometrial cancer includes a review of medical history and a general physical exam [7, 12, 14]. The following tests may help detect endometrial cancer:

19.4.1 Internal Pelvic Exam

This procedure is used to look for any lumps or changes in the shape of the uterus.

19.4.2 Pap Test (also called Pap Smear)

This test uses a microscopic exam of collected cells from the cervix to find any abnormal cells. Since endometrial cancer starts inside the uterus, it is not usually detected in the results of a Pap test.

19.4.3 Endometrial Biopsy

This method collects an endometrial tissue sample by inserting a thin, flexible tube through the cervix and into the uterus. A pathologist can view the tissue sample under a microscope to look if cancer or other abnormal cells are present.

19.4.4 Dilation and Curettage (Also Called D&C)

If the endometrial biopsy test result is unclear, a D&C procedure must be done. In this procedure, the cervix is dilated (opened, enlarged) so that the cervical canal and uterine lining can be scraped with a curette (a spoon-shaped special instrument) to collect the sample tissue from inside the uterus. The doctor examines the tissue for any cancer cells.

19.4.5 Transvaginal Ultrasound

This method is used to examine the vagina, uterus, fallopian tubes, and bladder. An ultrasound transducer (probe) is put into the vagina and used to bounce high-energy sound waves (ultrasound) from internal tissues or organs and make echoes. The echoes make an image (a picture) of body tissues (called a sonogram). The doctor can identify cancer if the uterus contains a mass (tumor), or if the endometrium is thicker than usual, which can be a sign of endometrial cancer. This procedure also helps detect if cancer is growing into the muscle layer of the uterus (myometrium).

19.5 Stages

Over time, endometrial cancer can potentially spread from the uterus to other parts of the body.

This cancer is classified into four stages based on how much it has grown or spread [8, 11]:

Stage 1: The cancer is only present in the uterus.

Stage 2: The cancer is present in the uterus and cervix.

Stage 3: The cancer has spread outside the uterus, but not as far as the rectum or bladder. It might be present in the fallopian tubes, ovaries, vagina, and/or nearby lymph nodes.

Stage 4: The cancer has spread beyond the pelvic area. It might be present in the bladder, rectum, and/or distant tissues and organs.

19.6 Methods of Treatment

There are several treatment options for patients with endometrial cancer currently available based on the patient's overall health, medical history, the extent of the disease, tolerance for specific therapies or procedures, expectations for the course, and opinion or preference [14–82].

Six types of standard treatment are used including surgery, radiation therapy, chemotherapy, targeted therapy, immunotherapy, and hormonal therapy.

19.6.1 Surgery

Doctors can remove tumors surgically. There are several types of surgical procedures available [21, 24].

19.6.1.1 Hysterectomy

This procedure is used to remove the uterus surgically.

19.6.1.2 Salpingo-oophorectomy

This procedure uses an operation to remove the fallopian tubes and ovaries.

19.6.1.3 Pelvic Lymph Node Dissection

This procedure removes some lymph nodes from the pelvis.

19.6.1.4 Para-aortic Lymphadenectomy

This procedure is used to remove the lymph nodes that surround the aorta, the main artery of the heart.

19.6.1.5 Laparoscopic Lymph Node Sampling

This method is used to remove the lymph nodes through a narrow viewing tube called a laparoscope, which is put through a small incision (cut) in the abdomen (belly).

19.6.1.6 Sentinel Lymph Node Mapping

This method uses fluorescent imaging to identify potentially cancerous lymph nodes that would otherwise go undetected.

19.6.2 Radiation Therapy

This procedure uses high-energy X-rays or gamma rays or charged particles or other types of radiation to kill cancer cells.

There are two types of radiation therapy used to treat endometrial cancer:

19.6.2.1 External Radiation Therapy

This radiation therapy uses a machine outside the body to focus beams toward the uterus or the area of the body with cancer.

19.6.2.2 Internal Radiation Therapy

This procedure uses a radioactive substance sealed in needles or catheters and is placed directly inside the body, into the vagina or uterus, or near the cancer.

19.6.3 Chemotherapy

The common chemotherapy drugs for endometrial cancer include cisplatin, carboplatin, docetaxel, doxorubicin, liposomal doxorubicin, and paclitaxel [20, 21, 32, 37, 39].

19.6.4 Targeted Therapy

Lenvatinib and bevacizumab work by slowing the growth of new blood vessels by inhibiting vascular endothelial growth factor A (VEGF-A). Everolimus (Afinitor) and temsirolimus (Torisel) are mTOR inhibitors that can be used to treat endometrial cancer. The mTOR protein controls cell division and growth. Inhibiting this protein prevents the growth of new cancer cells leading to ultimate cell death (apoptosis).

19.6.5 Immunotherapy

Immunotherapy activates the immune system's natural ability to fight cancer. Immune checkpoint inhibitors pembrolizumab (Keytruda) and dostarlimab (Jemperli) are drugs that target PD-1, a protein on immune system cells called T cells, that are used to treat this type of cancer [40].

19.6.6 Hormone Therapy

This therapy removes hormones or blocks their action and stops cancer cells from growing using hormone-blocking drugs [14–18, 29, 36]. Some hormones cause certain types of cancer to grow and some hormones and drugs are used to reduce the production of hormones or block them from working permanently. The progesterone or drugs like medroxyprogesterone acetate (Provera) and megestrol acetate (Megace) are used to treat endometrial cancer. Two luteinizing hormone-releasing hormone agonists (LHRH agonists) goserelin (Zoladex) and leuprolide (Lupron) drugs are used to reduce estrogen levels in the ovary in women. Aromatase inhibitors letrozole (Femara), anastrozole (Arimidex), and exemestane (Aromasin) are used to reduce estrogen levels further or can stop the production of estrogen permanently.

19.7 Treatment Regimens

Systemic Therapy Regimens for Recurrent, Metastatic, or High-Risk Endometrial Carcinoma

Single-Agent Regimens

Bevacizumab

15 mg/kg IV on day 1

Repeat cycle every three weeks and continue until disease progression or prohibitive toxicity [52].

Cisplatin

50 mg/m² IV infusion over 60 minutes on day 1

Repeat cycle every 21 days for up to six cycles [53].

Carboplatin

400 mg/m² IV infusion over 30 minutes on day 1
Repeat cycle every 21 days for six cycles [54].

Docetaxel

70 mg/m² IV infusion over 60 minutes on days 1, 8, and 15
Repeat cycle every 28 days and continue until progression of the disease or adverse effects prohibit further therapy [55].

Doxorubicin

60 mg/m² IV on day 1
Repeat cycle every three weeks [56, 57].

Liposomal Doxorubicin

50 mg/m² IV over 60 minutes on day 1
Repeat cycle every 28 days and continue until disease progression or unacceptable toxicity [58].

Ifosfamide

Ifosfamide: 2 g/m² IV daily on days 1–3, given second
Mesna: 2 g IV prior to ifosfamide infusion, given first
Repeat cycle every 21 days for a maximum of eight cycles [59].

Megestrol acetate

80 mg orally twice daily
Continue until disease progression or unacceptable toxicity [60].

Paclitaxel

110–200 mg/m² IV infusion over three hours on day 1
or 250 mg/m² IV infusion over 24 hours on day 1, plus G-CSF, 5 µg/kg/day from days 2–12
Repeat cycle every three weeks [61, 62].

Albumin-bound Paclitaxel

260 mg/m² IV on day 1
Repeat cycle every three weeks.

Pembrolizumab

200 mg IV over 30 minutes on day 1
Repeat cycle every three weeks [80].

Temsirolimus

25 mg IV infusion over 30 minutes once per week
Repeat cycle every three weeks [63].

Topotecan

1.5 mg/m² IV daily on days 1–5 or 1.2 mg/m² for patients with prior pelvic radiation daily on days 1–5
Repeat cycle every three weeks [64].

Tamoxifen

20 mg orally twice daily

Continue until disease progression or intolerable toxicity [65].

Dostarlimab-gxly (for microsatellite instability–high condition and DNA mismatch repair–deficiency tumors (MSI-H/dMMR))

500 mg IV infusion over 30 minutes once every three weeks for four doses, then 1000 mg IV infusion over 60 minutes once every six weeks until disease progression, treatment discontinuation due to toxic effects, or patient withdrawal of consent [81].

Combination Regimens**Doxorubicin + Cyclophosphamide**

Doxorubicin: 60 mg/m² IV on day 1

Cyclophosphamide: 500 mg/m² IV on day 1

Repeat cycle every three weeks [66].

Doxorubicin + Cisplatin

Doxorubicin: 50 mg/m² IV on day 1

Cisplatin: 50 mg/m² IV infusion over 60 minutes on day 1

Repeat cycle every three weeks [67, 68].

Cisplatin + Ifosfamide (for carcinosarcoma)

Cisplatin: 20 mg/m² IV infusion over 20 minutes daily on days 1–4

Mesna: 120 mg/m² IV bolus starting dose followed by 1500 mg/m²/day for 24 hours on days 1–4

Ifosfamide: 1500 mg/m² IV infusion over three hours daily on days 1–4

Repeat cycle every 21 days for three cycles [69]

Paclitaxel + Ifosfamide

Paclitaxel: 135 mg/m² IV over three hours on day 1

Mesna: 120 mg/m² IV bolus starting dose followed by 1500 mg/m²/day IV infusion for 24 hours on days 1–4, during 12 hours beginning 15 minutes before the ifosfamide infusion

Ifosfamide: 1600 mg/m² daily IV on days 1–3

Repeat cycle every 21 days for a total of eight cycles [70]. G-CSF support at 5 µg/kg/day to be started on day 4.

Carboplatin + Paclitaxel

Carboplatin: AUC 5–7, IV infusion over 30 minutes on day 1

Paclitaxel: 175 mg/m² IV infusion over three hours on day 1

Repeat cycle every four weeks [43, 71, 82].

Carboplatin + Docetaxel

Carboplatin: AUC of 6, IV over 60 minutes on day 1
Docetaxel: 60–75 mg/m² IV over 60 minutes on day 1
Repeat cycle every 21 days for six cycles [72–74].

Gemcitabine + Docetaxel

Gemcitabine: 900 mg/m² IV over 90 minutes on days 1 and 8
Docetaxel: 100 mg/m² IV over one hour on day 8
Granulocyte-colony-stimulating factor (GCSF) 150 microgram/m² on days 9–15
Repeat cycle every three weeks [75].

Lenvatinib + Pembrolizumab

Lenvatinib: 20 mg orally once daily
Pembrolizumab: 200 mg IV on day 1
Repeat cycle every three weeks [76].

Everolimus + Letrozole

Everolimus: 10 mg orally once daily on days 1–28
Letrozole: 2.5 mg orally once daily on days 1–28
Repeat cycle every four weeks [50].

Cisplatin + Doxorubicin + Paclitaxel

Cisplatin: 50 mg/m² IV infusion over 50 minutes on day 1
Doxorubicin: 45 mg/m² IV on day 1
Paclitaxel: 160 mg/m² IV over three hours on day 2
Filgrastim: 5 µg/kg SC on days 3–12
Repeat cycle every three weeks until disease progression or unacceptable toxicity [67, 68].

CAP

Cyclophosphamide: 500 mg/m² IV on day 1
Doxorubicin (Adriamycin): 50 mg/m² IV on day 1
Cisplatin (Platinol): 50 mg/m² IV on day 1
Repeat cycle every three weeks [77].

Paclitaxel + Carboplatin + Bevacizumab

Paclitaxel: 175 mg/m² IV over three hours on day 1
Carboplatin: AUC of 5, IV over 30 minutes on day 1
Bevacizumab: 15 mg/kg IV on day 1
Repeat cycle every 21 days for up to eight cycles [78, 79].

19.8 Risk Factors of Endometrial Cancer

The following factors may increase the risk of developing endometrial cancer in women [19, 25–27, 31]:

- (i) Obesity
- (ii) Diet high in animal fat
- (iii) Family history of endometrial, ovarian, and/or colon cancers (hereditary nonpolyposis colorectal cancer)
- (iv) Starting monthly periods before age 12
- (v) Late menopause
- (vi) Infertility (inability to become pregnant)
- (vii) Never having been pregnant
- (viii) Have few or no children
- (ix) Taking tamoxifen for treatment or prevention of breast cancer
- (x) Have diabetes
- (xi) High blood pressure
- (xii) Hormonal imbalance, having too much estrogen, and not enough progesterone in the body
- (xiii) Estrogen replacement therapy for the treatment of effects of menopause
- (xiv) Personal history of breast cancer
- (xv) Personal history of ovarian cancer
- (xvi) Prior radiation therapy for pelvic cancer
- (xvii) Have a history of infertility, irregular periods, or abnormal cells in the endometrium
- (xviii) Personal history of polycystic ovary syndrome or atypical endometrial hyperplasia
- (xix) The risk for endometrial cancer increases as women get older, and it is most common in white women
- (xx) Any metabolic syndrome increases the risk of endometrial cancer.

19.9 Prevention

Most endometrial cancer cannot be prevented. But there are certain things women should do to lower their risk [30, 38]. Taking birth control lowers the risk, but first talk with a medical professional. Being healthy, eating well, and maintaining your weight regularly may help lower the risk.

Women with hereditary nonpolyposis colon cancer (HNPCC or lynch syndrome) might be at a very high risk of developing endometrial cancer [33]. Patients should discuss advantages and disadvantages of hormone therapy with their specialized doctors. Avoiding known risk factors and increasing protective factors may help prevent endometrial cancer.

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20

Penile Cancer

20.1 Introduction

Penile cancer generally occurs on the skin of the penis and the foreskin (the skin covering the head of the penis). Human papillomavirus (HPV) causes about one-third of penile cancer cases [1–11]. This cancer is a rare malignancy, 1 case per 100 000 men in developed countries; but in certain Asian, African, and South American countries, it represents up to 10% of male malignancies. The incidence of penile cancer has been decreasing in recent years due to improving worldwide health conditions, and the increasing prevalence of circumcision. If it is detected early, penile cancer is mostly curable [12–24]. There are primarily four types of penile cancer: squamous cell carcinomas, Merkel cell carcinoma, small cell carcinoma, and melanoma. Among them, around 95% of penile cancers are squamous cell carcinomas.

20.2 Symptoms of Penile Cancer

The most common symptoms of penile cancer are changes in the penis skin on the foreskin of uncircumcised men, on the penis tip (the glans), and on the shaft (Figure 20.1). Other symptoms include:

- (a) Changes in skin thickness or color
- (b) A rash or small crusty bumps on the penis
- (c) A lump on the penis
- (d) A bad-smelling discharge underneath the foreskin
- (e) A sore on the penis or bleeding
- (f) Swelling at the end of the penis
- (g) Lumps under the skin in the groin area
- (h) Redness, irritation, or a sore on the penis
- (i) A reddish, velvety rash under the foreskin
- (j) Flat, bluish-brown growths
- (k) Smelly discharge (fluid) or bleeding under the foreskin

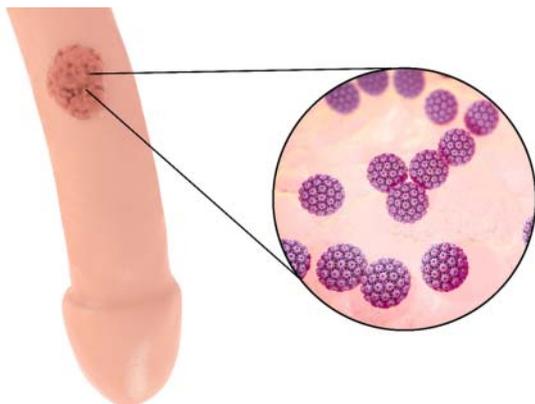


Figure 20.1 Penile cancer caused by human papillomavirus (HPV).

20.3 Penile Cancer Diagnosis

Diagnosis of penile cancer includes a review of medical history and a general physical exam. The doctor may recommend other tests, such as:

20.3.1 Biopsy

This procedure takes a small sample of tissue from a skin lesion on the penis. A pathologist can view the tissue sample under a microscope to look if cancer or other abnormal cells are present.

20.3.2 Imaging Tests

X-rays, CT scans, ultrasounds, and magnetic resonance imaging (MRI) tests can be done to confirm any cancer cells on the penis or other signs that cancer has spread.

20.4 Methods of Penile Cancer Treatment

There are several treatment options for patients with penile cancer currently available based on the patient's overall health, medical history, the extent of the disease, tolerance for specific therapies or procedures, expectations for the course, and opinion or preference [12, 14, 15, 17, 18].

Four types of standard treatment are used, such as surgery, radiation therapy, local treatment, chemotherapy, and systemic chemotherapy.

20.4.1 Surgery

The following types of surgery are used to remove tumors from the penis.

20.4.1.1 Circumcision

This procedure removes the foreskin and nearby skin.

20.4.1.2 Other Surgical Procedures

Mohs surgery [17] (microscopically controlled surgery), glansectomy, partial or total penectomy, lymph node surgery, sentinel lymph node biopsy (SLNB), and pelvic lymph node surgery are used to remove tumors.

20.4.2 Local Treatments (Other than Surgery) for Penile Cancer**20.4.2.1 Laser Ablation**

The doctor uses a beam of laser light to destroy (ablate) cancer cells.

20.4.2.2 Cryosurgery/Cryotherapy

This method uses liquid nitrogen to freeze and destroy cancer cells [20].

20.4.2.3 Photodynamic Therapy (PDT)

This method uses a special drug and laser light to kill the cancer cells near the surface of the penis.

20.4.3 Radiation Therapy

Radiation therapy uses high-energy rays or particles to kill cancer cells [21].

20.4.4 Chemotherapy

Two types of chemotherapy drugs are used for penile cancer:

20.4.4.1 Topical Chemotherapy

It is applied directly on the skin instead of taken by mouth or injected into the vein. 5-fluorouracil (5-FU) cream is used to treat this type of cancer. Imiquimod is also used as a cream to destroy cancer cells.

20.4.4.2 Systemic Chemotherapy

Systemic chemotherapy uses a drug by mouth or into a vein to kill the cancer cells.

Capecitabine, cisplatin, fluorouracil, paclitaxel, ifosfamide, bleomycin, methotrexate, paclitaxel, and mitomycin C were used as a single agent but moderate response rates were reported. Therefore, the combination of these drugs is used mostly [14, 26–43].

20.5 Treatment Regimens for Penile Cancer**Neoadjuvant Chemotherapy****Paclitaxel + Ifosfamide + Cisplatin (TIP)**

Paclitaxel (Taxol): 175 mg/m² IV over three hours on day 1

Ifosfamide: 1200 mg/m² IV over two hours once daily on days 1–3

Cisplatin (Paltinol): 25 mg/m² IV over two hours daily on days 1–3

Repeat cycle every three to four weeks for four cycles [14].

VBM

Vincristine: 1 mg IV once per day on days 1, 8, and 15
 Bleomycin: 15 mg IM once daily on days 1, 2, 8, 9, 15, and 16, given six hours and 24 hours after vincristine
 Methotrexate: 30 mg orally once per day on days 3, 10, and 17, given 48 hours after vincristine
 Repeat cycle every 21 days for four cycles [26, 27].

Adjuvant Chemotherapy**DCF**

Docetaxel: 75 mg/m² IV on day 1
 Cisplatin: 75 mg/m² IV on day 1
 5-fluorouracil: 750 mg/m²/day IV continuous infusion on days 1–4
 Repeat cycle every 21 days for four cycles [28].

Metastatic/Unresectable/Advanced Disease**BMP**

Bleomycin: 10 mg/m² IV bolus once daily on days 2–6
 Methotrexate: 25 mg/m² IV bolus once per day on days 1 and 8
 Cisplatin (Platinol): 75 mg/m² IV over one hour on day 1
 Repeat cycle every 21 days for six cycles [29–34].

Cisplatin + 5-fluorouracil

Cisplatin: 100 mg/m² IV once on day 1
 5-fluorouracil: 1000 mg/m²/day IV continuous infusion on days 1–5 (120 hours, total dose 5000 mg/m² per cycle) [35].

Cisplatin + Irinotecan

Cisplatin: 180 mg/m² IV over three hours once on day 1, given second
 Irinotecan: 60 mg/m² IV over 30 minutes once daily on days 1, 8, and 15, given first
 Repeat cycle every 28 days [36].

Paclitaxel + Cisplatin + 5-Fluorouracil

Paclitaxel: 120 mg/m² IV once on day 1, given first
 Cisplatin: 50 mg/m² IV once per day on days 1 and 2
 5-fluorouracil: 1000 mg/m²/day IV continuous infusion over 96 hours, started on day 2 (total dose per cycle is 4000 mg/m²)
 Repeat cycle every 21 days [27, 37].

TIP

Paclitaxel (Taxol): 175 mg/m² IV over three hours on day 1
 Ifosfamide: 1200 mg/m² IV over two hours on days 1–3
 Cisplatin (Paltinol): 25 mg/m² IV over two hours on days 1–3
 Repeat cycle every three to four weeks [14].

Single-Agent Regimens**Paclitaxel**

175 mg/m² IV over three hours once on day 1
 Repeat cycle every 21 days [38].

Panitumumab

200 mg IV once every three weeks
 Repeat cycle every 21 days for two years or until disease progression, unacceptable toxicity, or patient withdrawal [40–42].
 Cisplatin

Cetuximab

400 mg/m² IV loading dose on day 1 and then at 250 mg/m² IV weekly
 Continue treatment until disease progression, unacceptable toxicity, or patient withdrawal [43].
 Capecitabine

20.6 Risk Factors of Penile Cancer

Scientists do not know the exact causes of penile cancer. Certain risk factors may contribute to developing penile cancer [22–24]:

- (i) Have the HPV infection
- (ii) Over age 60
- (iii) Cigarette smoking and tobacco use
- (iv) Have a weakened immune system because of HIV or AIDS
- (v) Had psoriasis treatment with the drug psoralen and ultraviolet (UV) light

20.7 Penile Cancer Prevention

Cancer prevention is an action taken to lower the risk of getting cancer. Most penile cancer cannot be prevented. But there are certain things men should do to lower their risk [22, 44].

- (i) Have a circumcision, it is easier to keep the area clean.
- (ii) If men have a foreskin, make sure to carefully clean underneath it daily.

- (iii) Use safe sex practices to avoid HPV and HIV infections. Use condoms when having any kind of sex to lower your chances of getting HPV
- (iv) Take HPV vaccine Gardasil or Cervarix

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21

Testicular Cancer

21.1 Introduction

Testicles (testes; one is called a testis) are two organs each normally a little smaller than a golf ball (egg-shaped organs or walnut-shaped glands or oval-shaped sex glands). They are located inside the scrotum, a loose bag of skin underneath the penis. The size of two testicles should almost be the same; one may be slightly larger than the other which is normal. Testicles have two main functions. They produce male hormones (androgens) such as testosterone and sperm. The sperm matures in the testicles, the male cells needed to fertilize a female egg cell to start a pregnancy. The hormone testosterone controls the sex drive in men. It also helps in the growth of muscle, bone, and body hair. Testicular cancer starts when malignant cells develop in the tissues of a testicle or in both testicles. It can occur at any age of a boy or man, but it is most often found in men aged 15–44 years. Testicular cancer is very rare and normally is curable, even when cancer has spread beyond the testicle or other parts of the body [1–51].

The two main types of testicular cancers are seminoma and non-seminoma. Seminoma starts from young germ cells and grows slowly. Almost 40% of testicular cancers are seminomas. Non-seminoma occurs from more mature germ cells and it is more aggressive. Some testicular cancers may be a blend of both seminoma and non-seminoma (Figure 21.1).

21.2 Symptoms of Testicular Cancer

Signs and symptoms of testicular cancer include:

- (i) A lump or enlargement in one testicle or both testicles
- (ii) A feeling of heaviness in the scrotum
- (iii) A dull ache in the abdomen or groin area
- (iv) A sudden collection of fluid in the scrotum
- (v) Pain or discomfort in a testicle or the scrotum
- (vi) Enlargement or tenderness of the breasts
- (vii) Headaches or confusion, cancer may spread in the brain

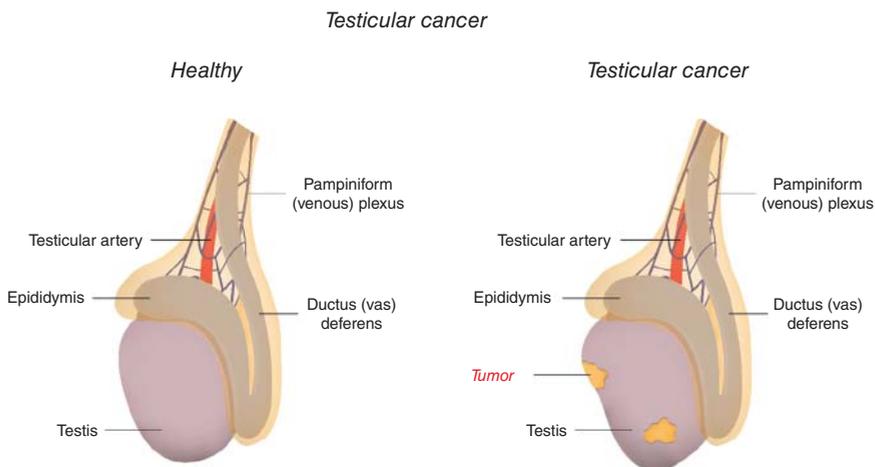


Figure 21.1 Normal testis and testis with cancer.

- (viii) Shortness of breath, chest pain, or cough with blood, cancer may spread in the lungs
- (ix) Belly pain, either from enlarged lymph nodes, possibly cancer, has spread to the liver.
- (x) Low back pain, possibly cancer, may spread to the lymph nodes in the back of the belly.

People with testicular cancer may experience a variety of symptoms or signs as not mentioned earlier. However, most people with testicular cancer do not have any of these symptoms or symptoms may be for a different medical condition, not related to cancer. Any symptom does not mean that a person has cancer.

21.3 Diagnosis

The following tests can help to diagnose testicular cancer:

21.3.1 Ultrasound

This procedure uses high-energy sound waves to create images of body tissues.

21.3.2 A Physical Exam and Medical History

Doctors can conduct a patient's physical exam and medical history related to testicular cancer.

21.3.3 Blood Tests for Tumor Markers

This procedure uses tumor markers and collects a blood sample to determine the amounts of certain proteins related to specific types of cancers. If alpha-fetoprotein

(AFP), human chorionic gonadotropin (HCG or beta-HCG), and lactate dehydrogenase (LDH) levels are increased that indicates a tumor on the testicle.

21.3.3.1 Biopsy

A tissue sample is collected from the testicles or nearby and checks under a microscope if cancer or other abnormal cells are present.

21.3.4 CT Scan and X-ray

CT scan and X-ray are used to determine the stages of cancer and if it has spread to the lymph nodes, lungs, liver, or other parts of the body.

21.4 Methods of Treatment

This cancer is highly treatable, even when cancer has spread to other parts of the body. Depending on the type and stage of testicular cancer, a patient may get one of several treatments or a combination. The three main kinds of treatment for testicular cancer are surgery, radiation therapy, and chemotherapy [35–54].

21.4.1 Surgical Treatment

Surgery to remove a testicle with cancer is referred to as radical inguinal orchiectomy. Retroperitoneal lymph node dissection (RPLND) is another method to remove lymph nodes around the large blood vessels (the aorta and inferior vena cava) at the back of the abdomen (belly).

21.4.2 Radiation Therapy

This method uses high-dose X-rays or particles to destroy cancer cells on the testis or nearby lymph nodes. It can be used after surgery for patients with seminomas to prevent the tumor from returning. Some forms of non-seminomas are resistant to radiation.

21.4.3 Chemotherapy

This method uses drugs such as Bleomycin Sulfate, Cisplatin, Dactinomycin, Etoposide, Ifosfamide, Paclitaxel, and Vinblastine to destroy cancer cells. This therapy has increased the survival rate for people with both seminomas and non-seminomas testicular cancer. High-Dose Chemotherapy and Stem Cell Transplant for Testicular Cancer might be used.

21.5 Treatment Regimens for Testicular Cancer

The cancer treatment protocol mentioned later may include both US Food and Drug Administration-approved and unapproved indications/regimens. These regimens

are provided as references to the current treatment strategies and educational purposes only. Doctors must select and verify treatment options based on the individual patient's physical condition.

Regimens for Metastatic Germ Cell Tumors

Carboplatin

Area under the Curve (AUC) of 7, IV over 30 minutes on day 1

Repeat cycle every 21 days for one to two cycles [42, 43].

Etoposide

50–100 mg/m² orally once daily on days 1–21

Repeat cycle every four weeks [41].

Cisplatin + Etoposide

Cisplatin: 20 mg/m² IV infusion over 30 minutes daily on days 1–5

Etoposide: 100 mg/m² IV infusion over 60 minutes daily on days 1–5

Repeat cycle every three weeks for up to four cycles [36].

BEP (or PEB)

Bleomycin: 30 units IV over 10 minutes on days 2, 9, and 16 or days 1, 8, and 15

Etoposide: 100 mg/m² IV over 90 minutes on days 1–5

Platinol (Cisplatin): 20 mg/m²/d IV over 60 minutes on days 1–5

Repeat cycle every 28 days for two cycles [44].

Pembrolizumab (for MSI-H/dMMR tumors or TMB-H tumors)

200 mg IV infusion over 30 minutes on day 1

Repeat cycle every 21 days [46, 47].

PVB

Cisplatin (Platinol): 20 mg/m² IV over 60 minutes daily on days 1–5

Vinblastine: 0.15 mg/kg IV on days 1 and 2

Bleomycin: 30 units IV over 10 minutes on days 2, 9, and 16

Repeat cycle every three weeks [48].

VeIP

Vinblastine (Velban): 0.11 mg/kg IV over 10 minutes on days 1 and 2

Ifosfamide: 1200 mg/m² IV over three hours daily on days 1–5

Cisplatin (Platinol): 20 mg/m² IV over 60 minutes daily on days 1–5

Mesna: 400 mg/m² IV, given 15 minutes before ifosfamide first dose, then 1200 mg/m² IV daily over three hours' continuous infusion on days 1–5

Repeat cycle every 21 days [49].

VIP (salvage therapy)

Etoposide (VP-16): 75 mg/m² IV over 60 minutes daily on days 1–5
 Ifosfamide: 1200 mg/m² IV over three hours daily on days 1–5
 Cisplatin (Platinol): 20 mg/m² IV over 60 minutes daily on days 1–5
 Mesna: 400 mg/m² IV over 15 minutes before ifosfamide first dose,
 then 1200 mg/m² IV daily over three hours' continuous
 infusion for five days

Repeat cycle every 21 days [37].

TIP (Salvage therapy)

Paclitaxel (Taxol): 250 mg/m² IV continuous infusion over 24 hours on day 1
 Ifosfamide: 1500 mg/m² IV infusion over three hours daily on days 2–5
 Cisplatin (Platinol): 25 mg/m² IV over 30 minutes daily on days 1–5
 Mesna: 500 mg/m² IV given before ifosfamide first dose, then at
 four and eight hours after ifosfamide on days 2–5

Repeat cycle every three weeks for four cycles [38].

Paclitaxel + Gemcitabine

Paclitaxel: 100 mg/m² IV over 60 minutes on days 1, 8, and 15
 Gemcitabine: 1000 mg/m² IV over 30 minutes on days 1, 8 and 15

Repeat cycle every four weeks for six cycles [39].

Gemcitabine + Oxaliplatin

Gemcitabine: 1000 mg/m² IV over 30 minutes on days 1 and 8
 Oxaliplatin: 130 mg/m² IV over two hours on day 1

Repeat cycle every three weeks [50, 51].

Gemcitabine + Paclitaxel + Oxaliplatin

Gemcitabine: 800 mg/m² IV over 30 minutes on days 1 and 8
 Paclitaxel: 80 mg/m² IV infusion over 60 minutes on days 1 and 8
 Oxaliplatin: 130 mg/m² IV infusion over two hours on day 1

Repeat cycle every three weeks for a total of eight cycles [40].

21.6 Risk Factors

Scientists do not know the exact causes of testicular cancer. Certain risk factors may contribute to the likelihood of developing testicular cancer.

21.6.1 An Undescended Testicle

Undescended testicle (cryptorchidism) is a condition when one or both testicles do not move into the scrotum before birth. This condition enhances the chance of developing testicular cancer. But it can be fixed if surgery is used before puberty.

21.6.2 Family History of Testicular Cancer

If your father or brother had testicular cancer, you have an increased likelihood of developing same cancer.

21.6.3 HIV Infection

Men with HIV infection have an increased risk of developing testicular cancer.

21.6.4 Race

White men (Caucasian men) are 5–10 times more likely to develop testicular cancer than men of other races and ethnicities.

21.6.5 Infertility

Infertile men have an increased risk of developing testicular cancer.

21.6.6 Certain Activities

Men with certain activities, such as bicycling, long-standing, and horseback riding, which regularly put pressure on the scrotum, have a higher likelihood of developing testicular cancer.

21.6.7 Reducing Exposure to Chemical Toxins

The exposure of phthalates and endocrine-disrupting compounds (hormone-mimicking chemicals) used regularly in many different household items such as carpets, plastics, toiletries, pesticides, pharmaceutical drugs, and car upholstery may cause testicular cancer.

21.7 Prevention

Several risk factors such as tobacco smoking, drinking alcohol, and not eating a cancer-fighting diet can be easily changed. But a man's age or family history cannot be changed; only detect early and take proper treatment. Moreover, cancer prevention is an action taken to lower the chance of getting cancer. Most testicular cancers cannot be prevented. But there are certain things men should do to lower their risk.

- (i) Building up your immune system
- (ii) Eating a cancer-fighting diet
- (iii) Taking supplements such as turmeric, medicinal mushrooms, and Boswellia
- (iv) Exercise regularly
- (v) Reducing stress

CHECK YOUR TESTICLES

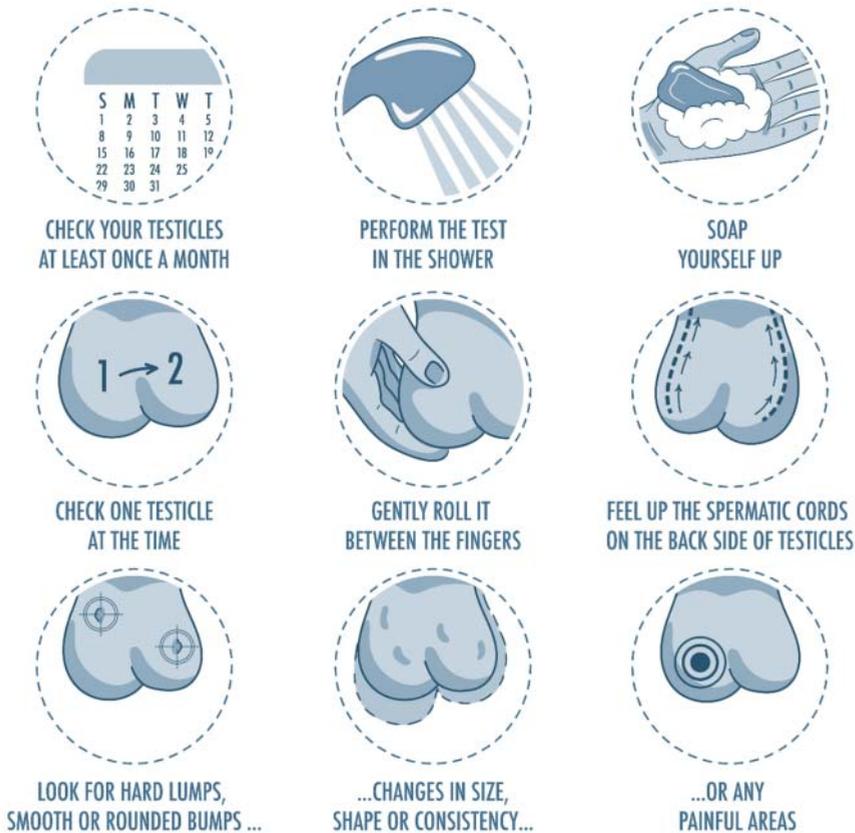


Figure 21.2 Self-examination of testicular cancer.

21.8 Self-Exam of Testicular Cancer

Stand in front of a mirror after a warm shower or bath. Examine for any changes or swelling on the skin of the scrotum and look at each testicle with both hands (Figure 21.2). If you find any pea-sized lumps which are painless, contact your doctor. If your son was born with an undescended testicle, contact his doctor for correcting it before he reaches puberty.

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