

CONTENTS

<i>Contributing Authors</i>	v
<i>Preface</i>	xxi
<i>Acknowledgments</i>	xxiii

PART I

Molecular Biology of Cancer

1. The Cancer Genome	2
----------------------------	---

Yarden Samuels, Alberto Bardelli, Yochai Wolf, and Carlos López-Otin

Introduction 2

Cancer Genes and Their Mutations 2

Identification of Cancer Genes 2

Somatic Alteration Classes Detected by Cancer Genome Analysis 9

Pathway-Oriented Models of Cancer Genome Analysis 11

Networks of Cancer Genome Projects 13

The Genomic Landscape of Cancers 15

Integrative Analysis of Cancer Genomics 15

Immunogenomics 16

The Cancer Genome and the New Taxonomy of Tumors 17

Cancer Genomics and Drug Resistance 20

Perspectives of Cancer Genome Analysis 21

Acknowledgments 21

2. Molecular Methods in Cancer.....	25
-------------------------------------	----

Larissa V. Furtado, Jay L. Hess, and Bryan L. Betz

Applications of Molecular Diagnostics in Oncology 25

The Clinical Molecular Diagnostics Laboratory: Rules and Regulations 29

Specimen Requirements for Molecular Diagnostics	29
Molecular Diagnostics Testing Process	29
Targeted Mutation Analysis Methods	30
Whole-genome Analysis Methods	36
Immunohistochemistry for Tumor Biomarkers	39
Cell-Free DNA Technologies	40
3. Hallmarks of Cancer: An Organizing Principle for Cancer Medicine.....	43
<i>Douglas Hanahan and Robert A. Weinberg</i>	
Introduction	43
Hallmark Capabilities, in Essence	43
Two Ubiquitous Characteristics Facilitate the Acquisition of Hallmark Capabilities	53
The Constituent Cell Types of the Tumor Microenvironment	55
Therapeutic Targeting of the Hallmarks of Cancer	61
Conclusion and a Vision for the Future	61
Acknowledgment	62
4. Microbiome and Cancer.....	66
<i>Giorgio Trinchieri</i>	
Introduction	66
Cancer as a Disease of the Metaorganism	66
Bacteria as Cause of Cancer	66
Bacteria as Cancer Drugs	70
Microbiota and Drug Metabolism	70
Microbiota and Chemotherapy	71
Microbiota and Immunotherapy	71
Looking Forward	74
5. Cancer Susceptibility Syndromes	77

Alice Hawley Berger and Pier Paolo Pandolfi

Introduction	77
Principles of Cancer Susceptibility	77
Genetic Testing	80
Cancer Susceptibility Syndromes	80
Principles of Cancer Chemoprevention	85
Emerging Knowledge and New Lessons	85
Conclusion	87

PART II

Etiology and Epidemiology of Cancer

SECTION 1. ETIOLOGY OF CANCER

6. Tobacco	90
------------------	----

Richard J. O'Connor

Introduction	90
Epidemiology of Tobacco and Cancer	90
Carcinogens in Tobacco Products and Processes of Cancer Development	92
Conclusion	96

7. Oncogenic Viruses	98
----------------------------	----

Christopher B. Buck, Lee Ratner, and Giovanna Tosato

Principles of Tumor Virology	98
Papillomaviruses	100
Polyomaviruses	102
Epstein-Barr Virus	104
Kaposi Sarcoma Herpesvirus	105
Animal and Human Retroviruses	107

Hepatitis Viruses	109
Conclusion	111
8. Inflammation.....	114
<i>Michael D. Green and Weiping Zou</i>	
Introduction	114
Tumor-Intrinsic Inflammation	114
Tumor-Extrinsic Inflammation	114
Inflammatory Cell Subsets in the Cancer Microenvironment	115
Inflammatory Molecular Mediators in Cancer	116
Cellular Mechanisms of Inflammation in Cancer	118
Molecular Mechanisms of Inflammation in Cancer	118
Inflammation as a Therapeutic Target	119
9. Chemical Factors	120
<i>Amanda K. Ashley and Christopher J. Kemp</i>	
Introduction	120
Initial Identification and Characterization of Carcinogens	120
Determining Carcinogenicity	121
Characteristics of Chemical Carcinogens	123
Outlook	124
10. Physical Factors	125
<i>Mats Ljungman</i>	
Introduction	125
Ionizing Radiation	126
Ultraviolet Light	128
Radiofrequency and Microwave Radiation	130

Electromagnetic Fields	130
Asbestos	130
Nanoparticles	131
11. Dietary Factors.....	133
<i>Karin B. Michels and Walter C. Willett</i>	
Introduction	133
Methodologic Challenges	133
The Role of Individual Food and Nutrients in Cancer Etiology	134
Other Foods and Nutrients	138
Dietary Patterns	140
Diet during Early Phases of Life	140
Diet after a Diagnosis of Cancer	141
The Microbiome	142
Summary	142
Limitations	142
Future Directions	143
Recommendations	143
12. Obesity and Physical Activity.....	145
<i>Justin C. Brown, Jeffrey A. Meyerhardt, and Jennifer A. Ligibel</i>	
Introduction	145
Obesity	145
Obesity and Cancer Risk	145
Obesity and Cancer Outcomes	145
Obesity and Cancer Treatment–Related Complications	146
Interventions	146
Physical Activity	147
Physical Activity and Cancer Risk	147

Physical Activity and Cancer Outcomes	148
Sedentary Behavior	148
Interventions	149
Mechanistic Data	149
Weight and Physical Activity Guidelines	149
American Society of Clinical Oncology Obesity Initiative	149
Conclusion	150

SECTION 2. EPIDEMIOLOGY OF CANCER

13. Epidemiologic Methods	152
---------------------------------	-----

Xiaomei Ma and Herbert Yu

Introduction	152
--------------	-----

Analytical Studies	152
--------------------	-----

Interpretation of Epidemiologic Findings	155
--	-----

Cancer Outcomes Research	155
--------------------------	-----

Molecular Epidemiology	156
------------------------	-----

14. Global Cancer Incidence and Mortality	160
---	-----

Ahmedin Jemal, Lindsey A. Torre, and Michael J. Thun

Introduction	160
--------------	-----

Geographic and Temporal Variations in Risk	160
--	-----

Data Sources	161
--------------	-----

Measures of Burden	161
--------------------	-----

Measures of Risk	164
------------------	-----

Demographic Factors that Affect Risk	165
--------------------------------------	-----

Temporal Trends	170
-----------------	-----

Incidence and Mortality Patterns for Common Cancers	173
---	-----

Issues in Interpreting Temporal Trends	180
--	-----

Conclusion	181
------------	-----

PART III

Cancer Therapeutics

15. Precision Medicine in Oncology.....186

James H. Doroshow

Introduction 186

Approach to Precision Medicine in Oncology 186

Preclinical Models to Inform Precision Oncology 188

Role of Molecular Pharmacodynamics and Diagnostics in Precision Oncology 189

Precision Oncology Clinical Trials and Trial Designs 190

Imaging and Precision Oncology 193

Precision Prevention 194

Future Prospects 194

16. Essentials of Radiation Therapy196

Meredith A. Morgan, Randall K. Ten Haken, and Theodore S. Lawrence

Introduction 196

Biologic Aspects of Radiation Oncology 196

Factors that Affect Radiation Response 201

Drugs that Affect Radiation Sensitivity 203

Radiation Physics 204

Treatment Planning 208

Other Treatment Modalities 210

Clinical Applications of Radiation Therapy 211

Treatment Intent 212

Fractionation 213

Adverse Effects 214

Principles of Combining Anticancer Agents with Radiation Therapy 215

17. Cancer Immunotherapy.....	218
-------------------------------	-----

Jeffrey Weber and Iulia Giuroiu

Introduction 218

Interferon- α 218

Interleukin-2 219

Talimogene Laherparepvec 220

Granulocyte Macrophage Colony-stimulating Factor 220

Tumor-Infiltrating Lymphocytes 221

Checkpoint Inhibitors—Cytotoxic T-Lymphocyte Antigen 4 and Programmed Cell Death Protein 1 221

Cytotoxic T-Lymphocyte Antigen 4 Blockade 223

Programmed Cell Death Protein 1 and Programmed Cell Death Protein Ligand 1 Blockade 223

Vaccines 227

Conclusion 227

18. Pharmacokinetics and Pharmacodynamics of Anticancer Drugs	231
---	-----

Alex Sparreboom and Sharyn D. Baker

Introduction 231

Pharmacokinetic Concepts 231

Pharmacodynamic Concepts 232

Variability in Pharmacokinetics/ Pharmacodynamics 233

Dose Adaptation Using Pharmacokinetic/Pharmacodynamic Principles 238

19. Pharmacogenomics	239
----------------------------	-----

Christine M. Walko and Howard L. McLeod

Introduction 239

Pharmacogenomics of Tumor Response	240
Pathway-Directed Anticancer Therapy	240
Genetic-Guided Therapy: Practical Issues in Somatic Analysis	242
Pharmacogenomics of Chemotherapy Drug Toxicity	243
Conclusions and Future Directions	244
20. Alkylating Agents	246
<i>Kenneth D. Tew</i>	
Historical Perspectives	246
Chemistry	246
Classification	246
Clinical Pharmacokinetics/Pharmacodynamics	250
Therapeutic Uses	251
Toxicities	252
Complications with High-Dose Alkylating Agent Therapy	253
Alkylating Agent–Steroid Conjugates	254
Drug Resistance and Modulation	254
Future Perspectives	254
21. Platinum Analogs.....	256
<i>Kim A. Reiss, A. Hilary Calvert, and Peter J. O'Dwyer</i>	
Introduction	256
History	256
Platinum Chemistry	257
Platinum Complexes after Cisplatin	257
Mechanism of Action	258
Cellular Responses to Platinum-Induced DNA Damage	259
Mechanisms of Resistance	260
Clinical Pharmacology	262

22. Antimetabolites	265
---------------------------	-----

James J. Lee and Edward Chu

Antifolates 265

5-Fluoropyrimidines 269

Capecitabine 271

Trifluridine/Tipiracil 271

Cytarabine 271

Gemcitabine 272

6-Thiopurines 273

Fludarabine 273

Cladribine 274

Clofarabine 274

23. Topoisomerase-Interacting Agents	276
--	-----

Anish Thomas, Khanh Do, Shivaani Kummar, James H. Doroshow, and Yves Pommier

Biochemical and Biologic Functions of Topoisomerases 276

Topoisomerase Inhibitors as Interfacial Poisons 276

Topoisomerase I Inhibitors: Camptothecins and Beyond 278

Topoisomerase II Inhibitors: Intercalators and Nonintercalators 281

Future Directions 285

24. Antimicrotubule Agents.....	288
---------------------------------	-----

Christopher J. Hoimes

Microtubules 288

Taxanes 288

Vinca Alkaloids 292

Microtubule Antagonists 294

Mitotic Motor Protein Inhibitors	294
Mechanisms of Resistance to Microtubule Inhibitors	295
Summary	295
25. Kinase Inhibitors as Anticancer Drugs	297
<i>Gopa Iyer, Debyani Chakravarty, and David B. Solit</i>	
Introduction	297
Validating Mutated Kinases as Cancer Drug Targets—the Development of Imatinib for Patients with Chronic Myelogenous Leukemia and Gastrointestinal Stromal Tumors	301
The Development of HER2-Targeted Therapies in Breast and Other Cancers	302
The Development of EGFR Tyrosine Kinase Inhibitors in Lung Cancer	303
Identifying Therapeutic Targets in EGFR Wildtype Lung Cancers	304
RAF and MEK Inhibitors for BRAF-Mutant Tumors	305
PI3 Kinase Pathway Inhibitors	307
One Target or Several: Multitargeted Kinase Inhibitor Therapy in Renal Cell Carcinoma and Medullary Thyroid Cancer	308
CDK4/6 Inhibitors	308
Bruton Tyrosine Kinase Inhibitors	309
A Potential Pan Cancer Drug Target—TRK Inhibitors	309
Future Directions	310
26. Histone Deacetylase Inhibitors and Demethylating Agents	312
<i>Stephen B. Baylin</i>	
Introduction	312
Epigenetic Abnormalities and Gene Expression Changes in Cancer	312
Histone Deacetylase Inhibitors	316
Epigenetic Therapy for Hematologic Malignancies	317
New Approaches to Epigenetic Therapy	318

27. Proteasome Inhibitors	320
---------------------------------	-----

Ajay K. Nooka, Vikas A. Gupta, Christopher J. Kirk, and Lawrence H. Boise

Biochemistry of the Ubiquitin-Proteasome Pathway 320

Proteasome Inhibitors 320

Proteasome Inhibitors in Cancer 322

28. Poly(ADP-Ribose) Polymerase Inhibitors for Tumors with Defects in DNA Repair	333
--	-----

Alan Ashworth

Introduction 333

Cellular DNA Repair Pathways 333

BRCA1 and *BRCA2* Mutations and DNA Repair 333

The Development of PARP Inhibitors 334

PARP-1 Inhibition as a Synthetic Lethal Therapeutic Strategy for the Treatment of
BRCA-Deficient Cancers 334

Initial Clinical Results Testing Synthetic Lethality of PARP Inhibitors and BRCA
Mutation 334

PARP Inhibitors Approved for Clinical Use 335

The Use of PARP Inhibitors in Non-*BRCA* Germline Mutant Cancers 335

Mechanisms of Resistance to PARP Inhibitors 335

Future Prospects 336

29. Miscellaneous Chemotherapeutic Agents.....	337
--	-----

M. Sitki Copur, Ryan Ramaekers, David Crockett, and Dron Gauchan

Homoharringtonine and Omacetaxine 337

L-Asparaginase 338

Bleomycin 338

Procarbazine 338

Dactinomycin	339
Vismodegib	339
Ado-Trastuzumab Emtansine	339
Sirolimus and Temsirolimus	340
Everolimus	340
Thalidomide, Lenalidomide, and Pomalidomide	341
Miscellaneous Agents with Potential for Repurposable Chemotherapeutic Use	342
30. Hormonal Agents	347
<i>Karthik V. Giridhar, Manish Kohli, and Matthew P. Goetz</i>	
Introduction	347
Selective Estrogen Receptor Modulators	347
Aromatase Inhibitors	351
Resistance to Endocrine-Targeted Therapy in Breast Cancer	352
Gonadotropin-Releasing Hormone Analogs	353
Antiandrogens	354
Resistance to Androgen Therapies in Prostate Cancer	355
Other Sex Steroid Therapies	356
Other Hormonal Therapies	356
31. Monoclonal Antibodies.....	359
<i>Hossein Borghaei, Matthew K. Robinson, Gregory P. Adams, and Louis M. Weiner</i>	
Introduction	359
Immunoglobulin Structure	359
Modified Antibody-Based Molecules	359
Factors Regulating Antibody-Based Tumor Targeting	359
Unconjugated Antibodies	361
Altering Signal Transduction	362
Immunoconjugates	362

Antibodies Approved for Use in Solid Tumors	363
Antibodies Used in Hematologic Malignancies	364
Conclusion	366
32. Immunotherapy Agents.....	369
<i>Jeffrey A. Sosman and Douglas B. Johnson</i>	
Introduction	369
Human Tumor Antigens	369
Tumor Vaccines	370
Oncolytic Viruses	377
Factors to Activate Immune Effector Cells	378
Signaling Modulation	379
Soluble Factors	380
Adenosine A _{2α} Receptor Axis	380
Innate Immune Modulation	381
Bifunctional Fusion Proteins	381
PART IV	
Cancer Prevention and Screening	
33. Tobacco Use and the Cancer Patient	388
<i>Graham W. Warren and Vani N. Simmons</i>	
Introduction	388
Tobacco Use Epidemiology, Addiction, and Tobacco Product Evolution	388
Electronic Nicotine Delivery Systems, or Electronic Cigarettes	388
Defining Tobacco Use by the Cancer Patient	389
Tobacco Use and Cessation by the Cancer Patient	390
Smoking Cessation in the Context of Lung Cancer Screening	390
The Clinical Effects of Smoking on Cancer Patients	390

Addressing Tobacco Use by the Cancer Patient 393
Research Considerations and the Future of Addressing Tobacco Use by Cancer Patients
398

34. Role of Surgery in Cancer Prevention	401
<i>José G. Guillem, Andrew Berchuck, Jeffrey A. Norton, Preeti Subhedar, Kenneth P. Seastedt, and Brian R. Untch</i>	
Introduction	401
Risk-Reducing Surgery in Breast Cancer	401
Hereditary Diffuse Gastric Cancer	403
Surgical Prophylaxis of Hereditary Ovarian and Endometrial Cancer	405
Multiple Endocrine Neoplasia Type 2	408
Hereditary Colorectal Cancer Syndromes: Familial Adenomatous Polyposis, <i>MUTYH</i> -Associated Polyposis, and Lynch Syndrome	412
35. Cancer Risk–Reducing Agents	419
<i>Dean E. Brenner and Scott M. Lippman</i>	
Why Cancer Prevention as a Clinical Oncology Discipline	419
Defining Cancer Risk–Reducing Agents (Chemoprevention)	420
Identifying Potential Cancer Risk–Reducing Agents	421
Preclinical Development of Cancer Risk–Reducing Agents	421
Clinical Development of Cancer Risk–Reducing Agents	422
Micronutrients	424
Anti-Inflammatory Drugs	429
Posttranslational Pathway Targets	431
Diet-Derived Natural Products	435
Anti-Infectives	436
36. Prophylactic Cancer Vaccines	444

John T. Schiller and Olivera J. Finn

Introduction	444
Overview of Infectious Agents in Cancer	445
Hepatitis B Vaccines	446
Human Papillomavirus Vaccines	447
Prospects for Prophylactic Vaccines against Other Oncogenic Microbes	448
Vaccines for Cancers of Noninfectious Etiology: Tumor-Specific and Tumor-Associated Target Antigens	450
Therapeutic Cancer Vaccines Have Set the Stage for Preventative Cancer Vaccines	451
Prophylactic Vaccines for Cancers of Noninfectious Etiology	452
37. Cancer Screening	454
<i>Otis W. Brawley and Howard L. Parnes</i>	
Introduction	454
Performance Characteristics of a Screening Test	455
Assessing a Screening Test	455
Screening Guidelines and Recommendations	457
Breast Cancer Screening	457
Gastrointestinal Tract Cancers	460
Gynecologic Cancer	462
Lung Cancer Screening	464
Prostate Cancer Screening	465
Skin Cancer Screening	467
38. Genetic Counseling.....	471
<i>Danielle C. Bonadies, Meagan B. Farmer, and Ellen T. Matloff</i>	
Introduction	471
Who Is a Candidate for Cancer Genetic Counseling?	472

Components of the Cancer Genetic Counseling Session	473
Issues in Cancer Genetic Counseling	477
Future Directions	481
Conclusion	482

PART V

Practice of Oncology

39. Design and Analysis of Clinical Trials	486
<i>Richard M. Simon</i>	
Introduction	486
Phase I Clinical Trials	486
Phase II Clinical Trials	487
Design of Phase III Clinical Trials	491
Factorial Designs	495
Analysis of Phase III Clinical Trials	496
Reporting Results of Clinical Trials	498
False-positive Reports in the Literature	498
Meta-analysis	499
40. Assessment of Clinical Response	501
<i>Susan Bates and Tito Fojo</i>	
Introduction	501
Assessing Response	501
Determining Outcome	505
41. Vascular Access	513
<i>Mohammad S. Jafferji and Stephanie L. Goff</i>	

Introduction 513	
Catheter Types 513	
External Catheters 513	
Implantable Devices 514	
Catheter Selection 516	
Pediatric Patients 516	
Insertion Techniques 516	
Catheter-Related Complications 517	
42. Endoscopic and Robotic Surgery.....	519
<i>Jeremy L. Davis, R. Taylor Ripley, and Jonathan M. Hernandez</i>	
Introduction 519	
Physiologic Effects of Endoscopic Surgery 520	
Applications of Endoscopic and Robotic Surgery 520	
Special Topics 522	
Gastrointestinal and Hepatopancreatobiliary Cancers 524	
Genitourinary and Gynecologic Oncology 525	
Emerging Techniques 526	
Conclusion 526	
43. Tumor Biomarkers	528
<i>Corey W. Speers and Daniel F. Hayes</i>	
Introduction 528	
Uses for Tumor Biomarker Tests 528	
What Are the Criteria to Incorporate a Tumor Biomarker Test into Clinical Practice? 530	
Tumor Biomarker Tests that Are Accepted for Routine Clinical Utility 534	
Special Circumstances 534	
Tumor Biomarker Tests of Radiation Response 534	
Conclusion 534	

SECTION 1. CANCER OF THE HEAD AND NECK

44. The Molecular Biology of Head and Neck Cancers 536

Thomas E. Carey, Mark E. Prince, and J. Chad Brenner

Incidence, Risk Factors, and Etiology 536

Oral Tongue Cancer in Young Patients 536

High-Risk HPV in Oropharyngeal Cancer 536

Molecular Mechanisms in HNSCC 537

The Cancer Genome Atlas Project 538

Inhibition of HNSCC Immune Escape 539

Cancer Stem Cells 539

45. Cancer of the Head and Neck 542

William M. Mendenhall, Peter T. Dziegielewski, and David G. Pfister

Incidence and Etiology 542

Anatomy and Pathology 542

Natural History 543

Diagnosis 543

Staging 544

Principles of Treatment for Squamous Cell Carcinoma 545

Management 545

NECK 546

Clinically Negative Neck 546

Clinically Positive Neck Lymph Nodes 547

Chemotherapy 547

General Principles of Combining Modalities 550

Chemotherapy as Part of Curative Treatment 551

Follow-up 556

ORAL CAVITY 556

Lip 556
Floor of the Mouth 557
Oral Tongue 559
Buccal Mucosa 560
Gingiva and Hard Palate (Including Retromolar Trigone) 561

OROPHARYNX 563

Anatomy 563
Pathology 563
Patterns of Spread 563
Clinical Picture 564
Staging 564
Treatment: Tonsillar Fossa 564
Results of Treatment: Tonsillar Area 566
Complications of Treatment: Tonsillar Area 567
Treatment: Base of Tongue 567
Results of Treatment: Base of Tongue 567
Follow-up: Base of Tongue 568
Complications of Treatment: Base of Tongue 568
Treatment: Soft Palate 568
Results of Treatment: Soft Palate 568
Complications of Treatment: Soft Palate 568

LARYNX 569

Anatomy 569
Pathology 569
Patterns of Spread 569
Clinical Picture 569
Differential Diagnosis and Staging 570
Treatment: Vocal Cord Carcinoma 570
Treatment: Supraglottic Larynx Carcinoma 572
Treatment: Subglottic Larynx Carcinoma 572
Treatment: Supraglottic Larynx Cancer 573

HYPOPHARYNX: PHARYNGEAL WALLS, PYRIFORM SINUS, AND POSTCRICOID PHARYNX 574

- Anatomy 574
- Pathology 574
- Patterns of Spread 574
- Clinical Picture 575
- Staging 575
- Treatment 575
- Results of Treatment 576
- Complications of Treatment 577
- NASOPHARYNX 577**
- Anatomy 577
- Pathology 577
- Patterns of Spread 577
- Clinical Picture 577
- Staging 578
- Treatment 578
- Results of Treatment 579
- Follow-up 579
- Complications of Treatment 579
- NASAL VESTIBULE, NASAL CAVITY, AND PARANASAL SINUSES 579**
- Anatomy 579
- Pathology 580
- Patterns of Spread 580
- Clinical Picture 581
- Staging 581
- Treatment 582
- Results of Treatment 583
- Complications of Treatment 583
- PARAGANGLIOMAS 584**
- Anatomy 584

Pathology	584
Patterns of Spread	584
Staging	584
Treatment	584
Results of Treatment	584
Complications of Treatment	584
MAJOR SALIVARY GLANDS	585
Anatomy	585
Pathology	585
Patterns of Spread	586
Clinical Picture	586
Differential Diagnosis	586
Staging	586
Treatment	586
Results of Treatment	587
Complications of Treatment	588
MINOR SALIVARY GLANDS	588
Anatomy	588
Pathology	588
Patterns of Spread	589
Clinical Picture	589
Treatment	589
Results of Treatment	589
46. Rehabilitation after Treatment of Head and Neck Cancer	598
<i>Douglas B. Chepeha and Teresa H. Lyden</i>	
Introduction	598
Pretreatment Counseling	598
Support during Treatment and Rehabilitation of the Chemoradiation Patient	598
Resources for Rehabilitation of Head and Neck Cancer Patients	605

SECTION 2. CANCER OF THE THORACIC CAVITY

47. The Molecular Biology of Lung Cancer 607

Jill E. Larsen and John D. Minna

Introduction 607

Genomics: Tools for Identification, Prediction, and Prognosis 607

Functional Genomics in Lung Cancer 609

Genetic and Epigenetic Alterations in Lung Cancer 610

Metastasis and the Tumor Microenvironment 614

Lung Cancers Stem Cells 615

Telomerase-Mediated Cellular Immortality in Lung Cancer 615

Clinical Translation of Molecular Data 615

48. Non–small-cell Lung Cancer 618

Anne Chiang, Frank C. Detterbeck, Tyler Stewart, Roy H. Decker, and Lynn Tanoue

Introduction 618

Incidence and Etiology 618

Anatomy and Pathology 622

Screening and Prevention 626

Diagnosis 628

Stage Evaluation 629

Management by Stage 631

Special Clinical Situations 654

Palliative Care 657

Conclusion 659

49. Small Cell and Neuroendocrine Tumors of the Lung 671

Christine L. Hann, M. Abraham Wu, Natasha Rekhtman, and Charles M. Rudin

Introduction	671
Small Cell Lung Cancer	671
Typical Carcinoid and Atypical Carcinoid Tumors	687
Large Cell Neuroendocrine Carcinoma	690
 50. Neoplasms of the Mediastinum	700
<i>Robert B. Cameron, Patrick J. Loehrer Sr., Alexander Marx, and Percy P. Lee</i>	
Thymic Neoplasms	700
Thymoma	700
Thymic Carcinoma	702
Germ Cell Tumors	707
 SECTION 3. CANCERS OF THE GASTROINTESTINAL TRACT	
51. Molecular Biology of the Esophagus and Stomach.....	713
<i>Anil K. Rustgi</i>	
Introduction	713
Molecular Biology of Esophageal Cancer	713
Molecular Biology of Gastric Cancer	715
 52. Cancer of the Esophagus.....	718
<i>Mitchell C. Posner, Karyn A. Goodman, and David H. Ilson</i>	
Introduction	718
Epidemiology	718
Etiologic Factors and Predisposing Conditions	718
Applied Anatomy and Histology	721
Natural History and Patterns of Failure	723
Clinical Presentation	723
Diagnostic Studies and Pretreatment Staging Tools	723

Staging Guidelines	724
Treatment	724
Predictors of Treatment Response	743
Palliation of Esophageal Cancer with Radiation Therapy	746
Radiotherapy Techniques	746
Treatment of Metastatic Disease	749
Stage-Directed Treatment Recommendations	753
53. Cancer of the Stomach.....	762
<i>Itzhak Avital, Aviram Nissan, Talia Golan, Yaacov Richard Lawrence, and Alexander Stojadinovic</i>	
Introduction	762
Anatomic Considerations	762
Pathology and Tumor Biology	763
Histopathology	763
Molecular Classification of Gastric Cancer	764
Patterns of Spread	764
Clinical Presentation and Pretreatment Evaluation	765
Pretreatment Staging	766
Staging, Classification, and Prognosis	767
Gastric Cancer Nomograms: Predicting Individual Patient Prognosis after Potentially Curative Resection	770
Treatment of Localized Disease	772
Technical Treatment-Related Issues	781
Treatment of Advanced Disease (Stage IV)	782
Surgery in Treatment of Metastatic Gastric Cancer	788
Gastric Cancer in the Elderly	789
54. The Molecular Biology of Pancreas Cancer	797
<i>Scott E. Kern and Ralph H. Hruban</i>	

Introduction	797
Common Genetic Changes in Pancreatic Ductal Adenocarcinoma	797
Less-Prevalent Genetic Changes in Pancreatic Ductal Adenocarcinoma	800
Other Neoplastic Lesions	801
 55. Cancer of the Pancreas.....	804
<i>Jordan M. Winter, Jonathan R. Brody, Ross A. Abrams, James A. Posey, and Charles J. Yeo</i>	
Incidence and Etiology	804
Anatomy and Pathology	805
Exocrine Pancreatic Cancers	805
Endocrine Pancreatic Cancers	809
Pancreatic Ductal Adenocarcinoma: Screening	809
Pancreatic Ductal Adenocarcinoma: Diagnosis	810
Pancreatic Ductal Adenocarcinoma: Staging	811
Stages I and II: Localized Pancreatic Ductal Adenocarcinoma	811
Stage III: Locally Advanced Disease	820
Emerging Role of Stereotactic Body Radiotherapy	824
Stage IV: Metastatic Disease	824
Future Directions and Challenges	829
Conclusion	830
 56. Molecular Biology of Liver Cancer.....	837
<i>Jens U. Marquardt and Snorri S. Thorgeirsson</i>	
Introduction	837
Genetic Alterations in Liver Cancer	837
Epigenetic Alterations in Liver Cancer	838
Mutational Landscape of Genetic Alterations—the Next Generation	839

The Microenvironment of Liver Cancer	839
Classification and Prognostic Prediction of Hepatocellular Carcinoma	841
Molecular Basis of Cholangiocarcinoma	842
Conclusion and Perspective	842
57. Cancer of the Liver	844
<i>Yuman Fong, Damian E. Dupuy, Mary Feng, and Ghassan Abou-Alfa</i>	
Introduction	844
Epidemiology	845
Etiologic Factors	845
Diagnosis	846
Staging	846
Treatment of Hepatocellular Carcinoma	847
Adjuvant and Neoadjuvant Therapy	850
Treatment of Other Primary Liver Tumors	861
58. Cancer of the Biliary Tree.....	865
<i>Tushar Patel and Kabir Mody</i>	
Introduction	865
Anatomy of the Biliary Tract	865
Cholangiocarcinoma	866
Gallbladder Cancer	877
Acknowledgments	881
59. Small Bowel Cancer	884
<i>Ronald Chamberlain, Nasrin Ghalyaie, and Sachin Patil</i>	
Introduction	884
Small Bowel Adenocarcinoma	886

Carcinoid Tumors	889
Small Bowel Lymphoma	891
Gastrointestinal Stromal Tumor	892
Metastatic Cancer to the Small Bowel	892
60. Gastrointestinal Stromal Tumor.....	895
<i>Paolo G. Casali, Angelo Paolo Dei Tos, and Alessandro Gronchi</i>	
Introduction	895
Incidence and Etiology	895
Anatomy and Pathology	895
Screening	898
Diagnosis	898
Staging	899
Management by Stage	900
Palliative Care	905
61. Molecular Biology of Colorectal Cancer.....	907
<i>Ramesh A. Shivdasani</i>	
Introduction	907
Multistep Models of Colorectal Cancer and Genetic Instability	907
Mutational and Epigenetic Landscapes in Colorectal Cancer	909
Insights from Mouse Intestinal Crypts and Human Colorectal Cancers Lead to a Coherent Model for Colorectal Cancer Initiation and Progression	910
Inherited Syndromes of Increased Cancer Risk Highlight Early Events and Critical Pathways in Colorectal Tumorigenesis	911
Oncogene and Tumor Suppressor Gene Mutations in Colorectal Cancer Progression	914
62. Cancer of the Colon	918
<i>Steven K. Libutti, Leonard B. Saltz, Christopher G. Willett, and Rebecca A. Levine</i>	

Introduction	918
Epidemiology	918
Etiology: Genetic, Environmental, and Other Risk Factors	919
Familial Colorectal Cancer	922
Anatomy of the Colon	923
Diagnosis of Colorectal Cancer	924
Screening for Colorectal Cancer	925
Staging and Prognosis of Colorectal Cancer	926
Approaches to Surgical Resection of Colon Cancer	933
Surgical Management of Complications from Primary Colon Cancer	935
Laparoscopic Colon Resection	936
Polyps and Stage I Colon Cancer	937
Stage II and Stage III Colon Cancer	937
Treatment of Stage II Patients	940
Treatment Options for Stage III Patients	942
Investigational Adjuvant Approaches	943
Follow-up after Management of Colon Cancer with Curative Intent	944
Surgical Management of Stage IV Disease	946
Management of Unresectable Metastatic Disease	946
Molecular Predictive Markers	961
 63. Cancer of the Rectum.....	970
<i>Steven K. Libutti, Christopher G. Willett, Leonard B. Saltz, and Rebecca A. Levine</i>	
Introduction	970
Anatomy	970
Staging	971
Surgery	974
Does Adjuvant Radiation Therapy Impact Survival?	981
Preoperative Radiation Therapy	982

Which Patients Should Receive Adjuvant Therapy?	984
Support of Nonoperative Management	985
Total Neoadjuvant Therapy	985
Concurrent Chemotherapy	987
Synchronous Rectal Primary and Metastases	989
Management of Unresectable Primary and Locally Advanced Disease (T4)	989
Management of Locally Recurrent Disease	990
Reirradiation in Recurrent Disease	990
Radiation Therapy Technique	990
Radiation Fields	991
64. Cancer of the Anal Region.....	997
<i>Brian G. Czito, Shahab Ahmed, Matthew F. Kalady, and Cathy Eng</i>	
Introduction	997
Epidemiology and Etiology	997
Screening and Prevention	998
Pathology	999
Clinical Presentation and Staging	1000
Prognostic Factors	1002
Treatment of Localized Squamous Cell Carcinoma	1002
Treatment of Other Sites and Pathologies	1009
SECTION 4. CANCERS OF THE GENITOURINARY SYSTEM	
65. Molecular Biology of Kidney Cancer.....	1014
<i>W. Marston Linehan and Laura S. Schmidt</i>	
Introduction	1014
Clear Cell Renal Cell Carcinoma	1014
Papillary Renal Cell Carcinoma	1015
Chromophobe Renal Cell Carcinoma	1018

Additional Types of Renal Cell Carcinoma 1018

Conclusion 1019

66. Cancer of the Kidney 1020

Andres F. Correa, Brian R. Lane, Brian I. Rini, and Robert G. Uzzo

Introduction 1020

Epidemiology, Demographics, and Risk Factors 1020

Pathology of Renal Cell Carcinoma 1020

Differential Diagnosis and Staging 1021

Hereditary Kidney Cancer Syndromes, Genetics, and Molecular Biology 1023

Treatment of Localized Renal Cell Carcinoma 1024

Treatment of Locally Advanced Renal Cell Carcinoma 1029

Surgical Management of Advanced Renal Cell Carcinoma 1031

Systemic Therapy for Advanced Renal Cell Carcinoma 1034

Conclusion and Future Directions 1038

Acknowledgments 1038

67. Molecular Biology of Bladder Cancer 1042

Carolyn D. Hurst and Margaret A. Knowles

Introduction 1042

Mutational Landscape 1042

Heterogeneity and Clonal Evolution 1045

Molecular Subtypes 1046

Therapeutic Opportunities and Future Outlook 1048

68. Cancer of the Bladder, Ureter, and Renal Pelvis 1050

Adam S. Feldman, Richard J. Lee, David T. Miyamoto, Douglas M. Dahl, and Jason A. Efstathiou

Introduction 1050	
Cancer of the Bladder 1053	
Cancers of the Renal Pelvis and Ureter 1067	
69. The Molecular Biology of Prostate Cancer	1076
<i>Charles Dai and Nima Sharifi</i>	
Introduction 1076	
The Genomic Landscape of Prostate Cancer 1076	
The Molecular Subtypes of Primary Prostate Cancer 1077	
The Clonal Evolution of Lethal Metastatic Prostate Cancer 1078	
Genetic Basis of Prostate Cancer Heritability 1078	
Androgen Signaling in Prostate Cancer 1079	
Other Signaling Pathways in Prostate Cancer 1082	
Areas of Ongoing Research and Emerging Therapeutic Approaches 1083	
Conclusion 1083	
70. Cancer of the Prostate	1087
<i>Michael J. Zelefsky, Michael J. Morris, and James A. Eastham</i>	
Introduction 1087	
Incidence and Etiology 1087	
Anatomy and Pathology 1089	
Diagnosis, Risk Assessment, and Stage Assignment 1093	
Management by Clinical States 1097	
Palliation 1126	
Future Directions 1127	
71. Cancer of the Urethra and Penis	1136
<i>J. Ryan Mark, Mark Hurwitz, and Leonard G. Gomella</i>	

Introduction	1136
Urethral Cancer in the Male	1136
Urethral Cancer in the Female	1138
Penile Cancer	1140
 72. Cancer of the Testis	1145

Matthew T. Campbell, Jose A. Karam, and Christopher J. Logothetis

Introduction	1145
Incidence and Epidemiology	1145
Initial Presentation and Management	1145
Histology	1146
Biology	1147
Immunohistochemical Markers	1149
Staging	1149
Management of Clinical Stage I Disease	1152
Management of Clinical Stage II Disease (Low Tumor Burden)	1154
Management of Stage II Disease with High Tumor Burden and Stage III Disease	1154
Management of Recurrent Disease	1157
Treatment Sequelae	1157
Long-term Follow-up	1158
Midline Tumors of Uncertain Histogenesis	1159
Other Testicular Tumors	1159

SECTION 5. GYNECOLOGIC CANCERS

73. Molecular Biology of Gynecologic Cancers.....	1163
---	------

Tanja Pejovic, Adam J. Krieg, and Kunle Odunsi

Introduction	1163
Ovarian Cancer	1163
Endometrial Cancer	1167

Cervix, Vaginal, and Vulvar Cancers 1168

74. Cancer of the Cervix, Vagina, and Vulva 1171

Patricia J. Eifel, Ann H. Klopp, Jonathan S. Berek, and Panagiotis A. Konstantinopoulos

Carcinoma of the Cervix 1171

Carcinoma of the Vagina 1193

Carcinoma of the Vulva 1198

75. Cancer of the Uterine Body 1211

Kaled M. Alektiar, Nadeem R. Abu-Rustum, and Gini F. Fleming

Endometrial Carcinoma 1211

Uterine Sarcomas 1222

76. Gestational Trophoblastic Neoplasia 1227

Donald P. Goldstein, Ross S. Berkowitz, and Neil S. Horowitz

Introduction 1227

Incidence 1227

Pathology and Natural History 1227

Indications for Treatment 1227

Measurement of Human Chorionic Gonadotropin 1227

Pretreatment Evaluation 1228

Staging and Prognostic Score 1228

Treatment 1229

Placental Site or Epithelioid Trophoblastic Tumors 1230

Subsequent Pregnancy after Treatment for Gestational Trophoblastic Neoplasia 1230

77. Ovarian Cancer 1232

Krishnansu S. Tewari, Richard T. Penson, and Bradley J. Monk

Incidence and Etiology	1232
Anatomy and Pathology	1233
Screening and Prevention	1234
Diagnosis	1235
Presentation and Evaluation of Advanced Disease	1236
International Federation of Gynecology and Obstetrics Staging	1237
Management by Stage	1238
Management of Newly Diagnosed Advanced-Stage Disease	1239
Management of Recurrent Disease	1244
Antiangiogenesis Therapy	1246
PARP Inhibitors	1248
Clinical Implications of <i>BRCA1/2</i> Mutation Status	1248
Olaparib	1249
Rucaparib	1250
Niraparib	1251
Veliparib	1252
Talazoparib	1252
<i>BRCA1/2</i> Reversion Mutations	1252
Tolerability of PARP Inhibitors	1252
Immunotherapy	1253
Therapeutic Vaccines	1254
Toll-Like Receptors	1254
Oncolytic Viruses	1254
Chimeric Antigen Receptors	1254
Bispecific T-Cell Engagers	1255
Immune-Mediated Toxicity	1255
Immune-Related Response Criteria	1255
SECTION 6. CANCER OF THE BREAST	
78. Molecular Biology of Breast Cancer	1259

Ana T. Nunes, Tara Berman, and Lyndsay Harris

Introduction	1259
Genetics of Breast Cancer	1259
Somatic Alterations in Breast Cancer	1261
Protein/Pathway Alterations	1265

79. Malignant Tumors of the Breast	1269
--	------

Reshma Jagsi, Tari A. King, Constance Lehman, Monica Morrow, Jay R. Harris, and Harold J. Burstein

Incidence and Etiology	1269
------------------------	------

Management of the High-Risk Patient	1271
-------------------------------------	------

Anatomy and Pathology	1272
-----------------------	------

Diagnosis and Biopsy	1277
----------------------	------

Staging	1277
---------	------

Management by Stage: Ductal Carcinoma In Situ	1281
---	------

Management by Stage: Primary Operable Invasive Breast Cancer	1283
--	------

Management by Stage: Adjuvant Systemic Therapy	1293
--	------

Management by Stage: Special Considerations	1299
---	------

Management by Stage: Metastatic Disease	1303
---	------

SECTION 7. CANCER OF THE ENDOCRINE SYSTEM

80. Molecular Biology of Endocrine Tumors	1317
---	------

Zeyad T. Sahli, Brittany A. Avin, and Martha A. Zeiger

Endocrine Syndromes	1317
---------------------	------

Adrenal Gland	1319
---------------	------

Parathyroid Gland	1321
-------------------	------

Pituitary Gland	1322
-----------------	------

Thyroid Gland	1322
---------------	------

Acknowledgments	1324
81. Thyroid Tumors	1326
<i>Anupam Kotwal, Caroline J. Davidge-Pitts, and Geoffrey B. Thompson</i>	
Anatomy and Physiology	1326
Thyroid Nodules	1326
Thyroid Tumor Classification and Staging Systems	1327
Differentiated Thyroid Cancer	1328
Treatment of Differentiated Thyroid Cancer	1329
Anaplastic Thyroid Carcinoma	1333
Medullary Thyroid Cancer	1333
Thyroid Lymphoma	1335
Children with Thyroid Carcinoma	1335
82. Parathyroid Tumors	1338
<i>Anupam Kotwal and Geoffrey B. Thompson</i>	
Incidence and Etiology	1338
Anatomy and Pathology	1338
Clinical Manifestations and Screening	1339
Diagnosis	1339
Staging	1340
Management of Parathyroid Cancer	1340
Follow-up and Natural History	1341
Prognosis	1341
83. Adrenal Tumors	1343
<i>Antonio M. Lerario, Dipika R. Mohan, Roy Lirov, Tobias Else, and Gary D. Hammer</i>	
Introduction	1343

Incidence and Etiology	1343
Anatomy and Pathology	1344
Screening	1346
Diagnosis	1346
Staging	1349
Management	1349
Palliative Care	1351
84. Pancreatic Neuroendocrine Tumors.....1352	
<i>James C. Yao, Callisia N. Clarke, and Douglas B. Evans</i>	
Introduction	1352
Incidence and Etiology	1353
Classification, Histopathology, and Molecular Genetics	1353
Diagnosis and Management of Pancreatic Neuroendocrine Tumors	1356
Cytotoxic Chemotherapy	1359
Functional Tumors	1361
Additional Clinical Considerations	1363
Small, Nonfunctioning, Sporadic Pancreatic Neuroendocrine Tumors	1365
85. Carcinoid Tumors and the Carcinoid Syndrome1368	
<i>Jeffrey A. Norton</i>	
Incidence and Etiology	1368
Anatomy and Pathology	1368
General Principles of Neuroendocrine Tumor Diagnosis, Staging, and Management	1368
Diagnosis, Staging, and Management by Primary Tumor Site	1370
Diagnosis and Management of Carcinoid Syndrome	1372
Antitumor Management	1373
Management of Liver Metastases	1375
Conclusions	1376

86. Multiple Endocrine Neoplasia	1377
--	------

Jeffrey A. Norton

Introduction 1377

Multiple Endocrine Neoplasia Type 1 1377

Multiple Endocrine Neoplasia Types 2 and 3 and Familial Medullary Thyroid Cancer

1380

Multiple Endocrine Neoplasia Type 4 1382

SECTION 8. SARCOMAS OF SOFT TISSUE AND BONE

87. Molecular Biology of Sarcomas	1384
---	------

Samuel Singer and Cristina R. Antonescu

Introduction 1384

Soft Tissue Sarcomas 1384

Bone and Cartilaginous Tumors 1393

Future Directions: Next-Generation Sequencing and Functional Screens 1394

88. Soft Tissue Sarcoma	1400
-------------------------------	------

Samuel Singer, William D. Tap, David G. Kirsch, and Aimee M. Crago

Introduction 1400

Incidence and Etiology 1400

Anatomic and Age Distribution and Pathology 1402

Clinical and Pathologic Features of Specific Soft Tissue Tumor Types 1403

Diagnosis and Staging 1414

Management by Presentation Status, Extent of Disease, and Anatomic Location 1418

Palliative Care 1438

Future Directions 1438

89. Sarcomas of Bone	1450
----------------------------	------

Richard J. O'Donnell, Steven G. DuBois, and Daphne A. Haas-Kogan

Introduction 1450

Incidence and Etiology 1451

Anatomy and Pathology 1451

Screening 1452

Diagnosis 1452

Staging 1456

Management by Diagnosis and Stage 1456

Continuing Care: Surveillance and Palliation 1468

SECTION 9. CANCERS OF THE SKIN

90. Cancer of the Skin.....	1475
-----------------------------	------

Sean R. Christensen, Lynn D. Wilson, and David J. Leffell

General Approach to Nonmelanoma Skin Cancer 1475

Basal Cell Carcinoma 1478

Squamous Cell Carcinoma and Actinic Keratosis 1483

Merkel Cell Carcinoma 1489

Dermatofibrosarcoma Protuberans 1491

Angiosarcoma 1493

Microcystic Adnexal Carcinoma 1494

Sebaceous Carcinoma 1494

Extramammary Paget Disease 1495

Atypical Fibroxanthoma 1495

91. Molecular Biology of Cutaneous Melanoma.....	1500
--	------

Michael A. Davies

Introduction 1500

The Cancer Genome Atlas Effort in Cutaneous Melanoma	1500
The RAS-RAF-MAPK Pathway	1501
Additional Oncogenic Pathways	1503
Melanin Synthesis Pathway	1506
Summary and Future Directions	1507
92. Cutaneous Melanoma.....	1510
<i>Antoni Ribas, Paul Read, and Craig L. Slingluff Jr.</i>	
Introduction	1510
Molecular Biology of Melanoma	1510
Epidemiology	1512
Changes in Incidence	1514
Sex and Age Distribution	1514
Melanoma in Children, Infants, and Neonates	1515
Anatomic Distribution	1515
Etiology and Risk Factors	1516
Prevention and Screening	1516
Diagnosis of Primary Melanoma	1518
General Considerations in Clinical Management of a Newly Diagnosed Cutaneous Melanoma (Stages I and II)	1522
Clinical Trials to Define Margins of Excision for Primary Cutaneous Melanomas	1523
Surgical Staging of Regional Nodes	1524
Selection of Patients for Sentinel Node Biopsy	1527
Management	1527
Thick Melanomas (T4A, T4B, >4 mm Thick)	1530
Special Considerations in Management of Primary Melanomas	1530
Primary Melanomas of the Fingers and Toes	1531
The Role of Radiation Therapy in the Management of Primary Melanoma Lesions	1531
Clinical Follow-up for Intermediate-Thickness and Thick Melanomas (Stage IB to IIC)	
	1531

Regionally Metastatic Melanoma (Stage III): Lymph Node Metastasis, Satellite Lesions, and In-Transit Metastases 1532

Management of Regional Metastases in Patients with Visceral or Other Distant Disease 1536

Adjuvant Systemic Therapy (Stages IIB, IIC, and III) 1537

Management of Distant Metastases of Melanoma (Stage IV) 1540

Radiation Therapy for Metastatic Melanoma (Stage IV) 1553

SECTION 10. NEOPLASMS OF THE CENTRAL NERVOUS SYSTEM

93. Molecular Biology of Central Nervous System Tumors 1561

Mark W. Youngblood, Jennifer Moliterno Günel, and Murat Günel

Introduction 1561

Pediatric Brain Tumors 1561

Adult Brain Tumors 1564

Summary 1566

Acknowledgments 1566

94. Neoplasms of the Central Nervous System 1568

Susan M. Chang, Minesh P. Mehta, Michael A. Vogelbaum, Michael D. Taylor, and

Manmeet S. Ahluwalia

Epidemiology of Brain Tumors 1568

Classification 1569

Anatomic Location and Clinical Considerations 1571

Neurodiagnostic Tests 1572

Surgery 1574

Radiation Therapy 1575

Chemotherapy and Targeted Agents 1578

Specific Central Nervous System Neoplasms 1578

Gliomatosis Cerebri 1587

Optic, Chiasmal, and Hypothalamic Gliomas	1587
Brain Stem Gliomas	1589
Cerebellar Astrocytomas	1590
Gangliogliomas	1591
Ependymoma	1592
Meningiomas	1593
Primitive Neuroectodermal or Embryonal Central Nervous System Neoplasms	1595
Pineal Region Tumors and Germ Cell Tumors	1598
Pituitary Adenomas	1600
Craniopharyngiomas	1601
Vestibular Schwannomas	1602
Glomus Jugulare Tumors	1604
Hemangioblastomas	1605
Chordomas and Chondrosarcomas	1606
Choroid Plexus Tumors	1607
Spinal Axis Tumors	1608

SECTION 11. CANCERS IN ADOLESCENTS AND YOUNG ADULTS

95. Adolescents and Young Adults with Cancer	1617
--	------

Archie Bleyer, Andrea Ferrari, Jeremy Whelan, and Ronald Barr

Epidemiology	1617
Etiology and Biology	1617
Signs, Symptoms, and Delays in Diagnosis	1620
Prevention and Screening	1622
Diagnosis	1623
Management	1623
Progress	1627
Future Challenges	1630

SECTION 12. LYMPHOMAS IN ADULTS

96. Molecular Biology of Lymphoma	1632
<i>Nicolò Compagno, Laura Pasqualucci, and Riccardo Dalla-Favera</i>	
Introduction	1632
The Cell of Origin of Lymphoma	1632
General Mechanisms of Genetic Alterations in Lymphoma	1634
Molecular Pathogenesis of B-Cell Non-Hodgkin Lymphoma	1635
Molecular Pathogenesis of T-Cell Non-Hodgkin Lymphoma	1642
Molecular Pathogenesis of Hodgkin Lymphoma	1643
97. Hodgkin Lymphoma	1648
<i>Anas Younes, Ahmet Dogan, Peter Johnson, Joachim Yahalom, John Kuruvilla, and Stephen Ansell</i>	
Introduction	1648
Pathology of Hodgkin Lymphoma	1648
Early-Stage Hodgkin Lymphoma	1654
Advanced-Stage Hodgkin Lymphoma	1657
Special Circumstances	1661
98. Non-Hodgkin Lymphoma	1671
<i>Arnold S. Freedman, Caron A. Jacobson, Andrea Ng, and Jon C. Aster</i>	
Introduction	1671
Incidence and Etiology	1671
Biology and Pathology	1672
Lymphoma Classification: the Principles of the World Health Organization Classification of Lymphoid Neoplasms	1676
Diagnosis, Staging, and Management	1677
Specific Disease Entities	1679
Mature T-Cell and Natural Killer Cell Neoplasms	1695

99. Cutaneous Lymphomas.....	1708
------------------------------	------

Francine M. Foss, Michael Girardi, and Lynn D. Wilson

Introduction 1708

Mycosis Fungoides and the Sézary Syndrome 1708

Epidemiology and Etiology 1708

Pathobiology 1708

Diagnosis and Staging 1710

The Sézary Syndrome 1710

Staging and Prognosis of Mycosis Fungoides and the Sézary Syndrome 1710

Clinical Evaluation of Patients with Cutaneous Lymphoma 1712

Principles of Therapy of Mycosis Fungoides and the Sézary Syndrome 1712

Skin-Directed Therapy 1714

Systemic Therapy for Mycosis Fungoides and the Sézary Syndrome 1715

Other Cutaneous Lymphomas 1717

100. Primary Central Nervous System Lymphoma	1721
--	------

Tracy T. Batchelor and Catherine H. Han

Epidemiology 1721

Histopathology and Molecular Profile 1722

Diagnosis 1722

Prognostic Models 1723

Management of Newly Diagnosed Primary Central Nervous System Lymphoma 1723

Treatment in the Elderly 1725

Management of Refractory/Relapsed Primary Central Nervous System Lymphoma 1725

Monitoring and Follow-up 1726

Neurotoxicity 1726

SECTION 13. LEUKEMIAS AND PLASMA CELL TUMORS

101. Molecular Biology of Acute Leukemias.....	1729
<i>Glen D. Raffel and Jan Cerny</i>	

Introduction	1729
Leukemic Stem Cell	1729
Elucidation of Genetic Events in Acute Leukemia	1729
Mutations Affecting Transcription Factors	1732
Mutations of Epigenetic Modifiers	1735
Mutations Affecting Signaling	1737
Mutations in Tumor Suppressor Genes	1738
Activating Mutations of NOTCH	1738
Mutations Altering Localization of NPM1	1739
Mutations in Cohesin Complex Genes	1739
Mutations in Splicing Machinery	1739
Mutational Complementation Groups in Acute Leukemias	1739
Conclusion	1740

102. Management of Acute Leukemias	1742
<i>Partow Kebriaei, Farhad Ravandi, Marcos de Lima, and Richard Champlin</i>	

Introduction	1742
Acute Myeloid Leukemia	1743
Acute Lymphoblastic Leukemia	1751

103. Molecular Biology of Chronic Leukemias	1764
<i>Christopher A. Eide, James S. Blachly, and Anupriya Agarwal</i>	

Introduction	1764
Chronic Myeloid Leukemia	1764
Chronic Lymphocytic Leukemia	1767
Acknowledgments	1770

104. Chronic Myeloid Leukemia	1773
-------------------------------------	------

Carlo Gambacorti-Passerini and Philipp le Coutre

Introduction 1773

Epidemiology and Pathogenesis 1773

Diagnosis 1774

Differential Diagnosis and Staging 1775

Prognostic Factors 1775

Therapy 1776

Assessment of Response to Tyrosine-Kinase Inhibitors 1778

Therapy of Chronic Phase Chronic Myeloid Leukemia 1778

Treatment of Advanced Disease 1781

Future Directions 1781

Acknowledgments 1782

105. Chronic Lymphocytic Leukemias.....	1785
---	------

William G. Wierda and Susan M. O'Brien

Introduction 1785

Immunophenotype 1785

Molecular Biology 1785

Immune Abnormalities 1786

Diagnosis 1787

Clinical Manifestations 1787

Laboratory Findings 1787

Autoimmune Complications 1788

Staging 1788

Indications for Treatment and Response Criteria 1789

Treatments for Chronic Lymphocytic Leukemia 1790

Management Recommendations 1796

Prolymphocytic Leukemia	1797
Large Granular Lymphocyte Leukemia	1798
Hairy Cell Leukemia	1798
 106. Myelodysplastic Syndromes	1802
<i>Rami S. Komrokji, Eric Padron, and Alan F. List</i>	
Introduction	1802
Historical Perspective	1802
Epidemiology	1802
Etiology	1802
Pathology	1803
Pathogenesis	1806
Clinical Presentation	1808
Risk Assessment and Prognosis	1808
Management of Myelodysplastic Syndromes	1810
 107. Plasma Cell Neoplasms.....	1818
<i>S. Vincent Rajkumar and Shaji Kumar</i>	
Introduction	1818
Multiple Myeloma	1818
Pathogenesis	1820
Cytogenetic Classification	1822
Clinical Features	1823
Diagnostic Tests	1823
Differential Diagnosis	1825
Staging and Risk Stratification	1825
Prognosis	1825
Treatment	1826
Supportive Care	1837

MONOCLONAL GAMMOPATHY OF UNDETERMINED SIGNIFICANCE 1839

Introduction 1839

Incidence and Prevalence 1839

Clinical Features 1839

Differential Diagnosis 1839

Prognosis 1839

Risk Stratification 1841

Management 1841

SMOLDERING MULTIPLE MYELOMA 1841

Introduction 1841

Prevalence 1841

Clinical Features 1841

Differential Diagnosis 1841

Prognosis 1842

Risk Stratification 1842

Management 1842

Waldenström Macroglobulinemia 1844

Diagnosis 1844

Prognosis 1844

Treatment 1844

Systemic AL (Immunoglobulin Light Chain) Amyloidosis 1845

Diagnosis 1846

Prognosis 1847

Treatment 1847

Solitary Plasmacytoma 1848

Diagnosis and Prognosis 1848

Treatment 1848

POEMS Syndrome 1848

SECTION 14. OTHER CANCERS

108. Cancer of Unknown Primary	1856
--------------------------------------	------

Sarah Yentz, Manali Bhave, Erin Cobain, and Laurence Baker

Introduction	1856
Pathology Evaluation	1856
Additional Pathologic Diagnostic Tests in Cancers of Unknown Primary	1856
Use of Next-Generation Sequencing	1858
Clinical Features and Evaluation	1859
Prognostic Factors	1862

109. Benign and Malignant Mesothelioma 1863

Harvey I. Pass, Michele Carbone, Lee M. Krug, and Kenneth E. Rosenzweig

Introduction	1863
Epidemiology	1863
Mechanism of Asbestos Carcinogenesis	1863
Mechanism of Asbestos Pathogenicity	1864
Overview of Molecular Mechanisms in Mesothelioma	1864
Genetic Predisposition to Mesothelioma: BAP1	1866
Pathology of Mesothelioma	1866
Clinical Presentation	1867
Diagnostic Approach for Presumed Mesothelioma	1871
Natural History	1871
Treatment	1874
Palliation or Macroscopic Complete Resection	1875
Chemotherapy	1878
Novel Therapeutic Approaches	1880
Radiotherapy for Mesothelioma	1882

110. Peritoneal Metastases and Peritoneal Mesothelioma 1889

Alvaro Arjona-Sanchez, Marcello Deraco, Olivier Glehen, David Morris, and Paul H. Sugarbaker

Introduction 1889	
Natural History Studies Document the Importance of Local-Regional Progression 1890	
Patient Selection Using Quantitative Prognostic Indicators 1890	
Appendiceal Malignancy 1892	
Colorectal Peritoneal Metastases: Curative Treatment and Prevention 1893	
Malignant Peritoneal Mesothelioma 1894	
Gastric Cancer 1895	
Peritoneal Metastases in Ovarian Cancer 1895	
Sarcomatosis 1896	
 111. Intraocular Melanoma.....	1899

Paul T. Finger and Anna C. Pavlick

Introduction 1899	
Incidence and Etiology 1899	
Anatomy and Pathology 1899	
Ophthalmic Diagnosis 1900	
Staging 1902	
Management of Primary Uveal Melanoma 1902	
Overview: Treatment of Uveal Melanoma 1902	
Treatment for Special Cases 1904	
Diagnosis of Metastasis 1904	
Biomarkers: Prognostic and Predictive Factors 1907	
Summary 1908	

SECTION 15. ONCOLOGIC EMERGENCIES

112. Superior Vena Cava Syndrome.....	1910
---------------------------------------	------

Andreas Rimner and Joachim Yahalom

Introduction 1910	
-------------------	--

Anatomy and Pathophysiology	1910
Clinical Presentation and Etiology	1910
Diagnostic Workup	1912
Disease-Specific Management and Outcomes	1912
Small-cell Lung Cancer	1912
Non–small-cell Lung Cancer	1913
Non-Hodgkin Lymphoma	1913
Nonmalignant Causes	1913
Catheter-Induced Obstruction	1913
Treatment	1913
Areas of Uncertainty	1914
Recommendations	1914
113. Increased Intracranial Pressure	1915
<i>Ashley M. Roque and Joachim M. Baehring</i>	
Introduction	1915
Pathophysiologic Considerations	1916
Epidemiology and Pathogenesis	1916
Clinical Presentation	1917
Diagnosis	1918
Treatment	1920
114. Spinal Cord Compression	1921
<i>Nicholas Szerlip, Whitney H. Beeler, and Daniel E. Spratt</i>	
Incidence and Etiology	1921
Anatomy and Pathophysiology	1922
Clinical Presentation	1922
Differential Diagnosis	1922
Diagnosis	1922

Grading 1923

Management by Stage 1923

115. Metabolic Emergencies.....1928

Stacey Stein and Hari A. Deshpande

Introduction 1928

Tumor Lysis Syndrome and Hyperuricemia 1928

Hyponatremia 1929

Hypercalcemia 1930

Lactic Acidosis 1931

Hyperammonemia 1931

Summary 1932

SECTION 16. TREATMENT OF METASTATIC CANCER

116. Metastatic Cancer to the Brain.....1934

John H. Suh, Rupesh Kotecha, Manmeet S. Ahluwalia, and Michael A. Vogelbaum

Introduction 1934

Epidemiology 1934

Clinical Presentation 1934

Imaging and Diagnosis 1934

Prognosis 1934

Symptom Management 1935

Treatment Options 1936

Leptomeningeal Metastases 1941

117. Metastatic Cancer to the Lung1946

John Yonge and Jessica Donington

Introduction 1946

Presentation and Diagnosis of Pulmonary Metastases	1946
Surgical Metastasectomy	1947
Ablative Therapies	1950
Treatment Concerns and Outcomes for Individual Histologies	1951
Conclusion	1954
 118. Metastatic Cancer to the Liver.....	1957
<i>Clifford S. Cho, Sam Lubner, and Dawn Owen</i>	
Introduction	1957
Hepatic Colorectal Adenocarcinoma Metastases	1960
Hepatic Neuroendocrine Carcinoma Metastases	1965
Noncolorectal Nonneuroendocrine Hepatic Metastases	1967
 119. Metastatic Cancer to the Bone	1970
<i>Edward Chow, Joel A. Finkelstein, Arjun Sahgal, and Robert E. Coleman</i>	
Introduction	1970
Presentation	1970
Pathophysiology	1970
Diagnostic Evaluation	1970
Therapeutic Modalities	1970
Optimum Use of Bone-Targeted Agents in Metastatic Bone Disease	1971
New Targeted Therapies in the Treatment of Metastatic Bone Disease	1972
External-Beam Radiation Therapy	1972
Systemic Radionuclides	1974
Radiotherapy for Complications of Bone Metastases: Localized External-Beam	
Radiotherapy for Pathologic Fractures	1974
 120. Malignant Pleural and Pericardial Effusions	1983
<i>R. Taylor Ripley</i>	

Malignant Pleural Effusions 1983

Treatment Algorithm 1987

Malignant Pericardial Effusions 1987

Summary 1989

121. Malignant Ascites 1991

Thuy B. Tran and Ajay V. Maker

Incidence and Etiology 1991

Anatomy and Pathology 1991

Diagnosis 1991

Management 1992

122. Paraneoplastic Syndromes 1998

Daniel Morgensztern, Saiama N. Waqar, and Ramaswamy Govindan

Introduction 1998

Paraneoplastic Neurologic Syndromes 1998

Paraneoplastic Endocrinology Syndromes 2000

Paraneoplastic Hematologic Syndromes 2003

Paraneoplastic Dermatologic Manifestations 2004

Paraneoplastic Rheumatologic Manifestations 2005

SECTION 17. STEM CELL TRANSPLANTATION

123. Autologous Hematopoietic Cell Transplantation..... 2008

Hillard M. Lazarus, Mehdi Hamadani, and Parameswaran N. Hari

Introduction 2008

Autologous Hematopoietic Progenitor Cell Collection 2008

Autologous Hematopoietic Cell Transplantation Toxicities and Supportive Care 2008

Autologous Hematopoietic Cell Transplantation for Plasma Cell Myeloma	2009
Older Patients and Those with Comorbidities	2012
Maintenance Therapy after Hematopoietic Cell Transplantation	2012
Tandem Autologous Hematopoietic Cell Transplantation	2012
Response and Minimal Residual Disease after HCT	2012
Unique Considerations for Hematopoietic Progenitor Cell Collection in Myeloma	2012
Salvage Second or Third Transplants at Relapse	2013
Future Directions in Autologous Hematopoietic Cell Transplantation for Myeloma	2013
Autologous Hematopoietic Cell Transplantation for Rare Plasma Cell Dyscrasias	2013
Autologous Hematopoietic Cell Transplantation for Lymphomas	2013
Hematopoietic Cell Transplantation for Follicular Lymphoma	2013
Hematopoietic Cell Transplantation for Mantle Cell Lymphoma	2015
Hematopoietic Cell Transplantation for Waldenström Macroglobulinemia	2015
Hematopoietic Cell Transplantation for Marginal Zone and Small Lymphocytic Lymphoma	2015
Hematopoietic Cell Transplantation for Diffuse Large B-Cell Lymphoma	2015
Hematopoietic Cell Transplantation for Burkitt Lymphoma	2015
Hematopoietic Cell Transplantation for Hodgkin Lymphoma	2016
Hematopoietic Cell Transplantation for T-Cell Lymphomas	2016
Unique Considerations for Hematopoietic Cell Transplantation Mobilization in Lymphomas	2016
Tumor Cell Contamination in Autograft	2016
Posttransplantation Maintenance Therapies for Lymphoid Malignancies	2016
Functional Imaging and Autologous Hematopoietic Cell Transplantation Outcomes	2016
Autologous Hematopoietic Cell Transplantation for Acute Myeloid Leukemia	2016
Autologous Hematopoietic Cell Transplantation for Acute Lymphoblastic Leukemia	2017
Autologous Hematopoietic Cell Transplantation for Germ Cell Tumors	2017
Late Complications after Autologous Hematopoietic Cell Transplantation	2017
124. Allogeneic Stem Cell Transplantation	2019

Stanley R. Riddell and Edus H. Warren

Introduction 2019

Conditioning Regimens 2019

Stem Cell Sources 2020

Immunobiology of Allogeneic Hematopoietic Cell Transplantation 2023

Complications of Allogeneic Hematopoietic Cell Transplantation and Their Management

2024

Graft Failure 2028

Outcome of Allogeneic Hematopoietic Cell Transplantation for Hematologic

Malignancies and Solid Tumors 2028

Management of Posttransplant Relapse 2032

Future Directions 2032

SECTION 18. MANAGEMENT OF ADVERSE EFFECTS OF TREATMENT

125. Infections in the Cancer Patient 2036

Tara N. Palmore, Mark Parta, Jennifer Cuellar-Rodriguez, and Juan C. Gea-Banacloche

RISK FACTORS FOR INFECTIONS IN PATIENTS WITH CANCER AND

ANTIMICROBIAL PROPHYLAXIS 2036

Risk Factors for Infection 2036

Prevention of Infections 2041

DIAGNOSIS AND MANAGEMENT OF INFECTIOUS DISEASES SYNDROMES

2043

Fever and Neutropenia 2043

Multidrug-Resistant Organisms of Interest in Oncology 2059

126. Neutropenia and Thrombocytopenia 2068

Lodovico Balducci, Bijal Shah, and Kenneth Zuckerman

Introduction 2068

127. Nausea and Vomiting.....	2077
-------------------------------	------

Elizabeth M. Blanchard and Paul J. Hesketh

Introduction 2077

Nausea and Vomiting Syndromes 2077

Pathophysiology of Treatment-Induced Nausea and Vomiting 2077

Defining the Risk of Nausea and Vomiting 2078

Antiemetic Agents 2079

Lower Therapeutic Index 2082

Antiemetic Treatment by Clinical Setting 2082

Special Chemotherapy-Induced Nausea and Vomiting Problems 2083

Radiotherapy-Induced Nausea and Vomiting 2083

128. Diarrhea and Constipation	2085
--------------------------------------	------

Nathan I. Cherny and Batsheva Werman

Introduction 2085

Diarrhea 2085

Neutropenic Colitis 2086

Ischemic Colitis (Nonneutropenic Enterocolitis) 2087

Targeted Therapy–Associated Diarrhea 2087

Immunotherapy-Associated Diarrhea 2087

Radiotherapy-Induced Diarrhea 2087

Other Causes of Treatment-Related Diarrhea 2087

Assessment 2088

General Principles in the Management of Diarrhea 2088

Antidiarrhea Medications 2088

Specific Management Guidelines 2089

Radiation Therapy–Induced Diarrhea 2089

Immunotherapy-Induced Diarrhea and Colitis 2089

Management of Neutropenic Enterocolitis	2090
Diarrhea Prophylaxis	2090
Constipation	2090
Conclusion	2093
129. Oral Complications	2094
<i>Jane M. Fall-Dickson, Stefan Cordes, and Ann M. Berger</i>	
Introduction	2094
Oral Mucositis	2094
Radiation Therapy–Related Complications	2095
Pathogenesis of Chemotherapy- and Radiation Therapy–Induced Oral Mucositis	2095
Chronic Graft-Versus-Host Disease Oral Manifestations	2096
Sequelae of Oral Complications	2097
Strategies for Prevention and Treatment of Oral Complications	2097
Treatment Strategies	2098
Radioprotectors	2099
Biologic Response Modifiers	2100
Treatment for Oral Chronic Graft-Versus-Host Disease	2103
Symptom Management	2103
130. Pulmonary Toxicity	2109
<i>Diane E. Stover, Michael T. Bender, Manju V. Pillai, and Robert J. Kaner</i>	
Introduction	2109
Radiation-Induced Pulmonary Toxicity	2109
Chemotherapy-Induced Pulmonary Toxicity	2111
Additional Resources	2118
131. Cardiac Toxicity.....	2119
<i>Joachim Yahalom and Matthew A. Lunning</i>	

Introduction	2119
Chemotherapeutics	2119
Radiotherapy-Associated Cardiac Sequelae	2123
Conclusion	2126
132. Hair Loss and Other Hair Changes	2128
<i>Hoyoung M. Maeng and Ann M. Berger</i>	
Introduction	2128
Anatomy and Physiology of Hair	2128
Classification of Hair Loss	2129
Diagnosis of Hair Loss	2129
Treatment and Prevention of Chemotherapy-Induced Hair Loss	2130
Radiation-Induced Hair Changes	2131
Other Hair-Associated Changes	2131
Future Considerations	2132
133. Gonadal Dysfunction	2133
<i>George Patounakis, Alicia Y. Christy, and Alan H. DeCherney</i>	
Introduction	2133
Effects of Cytotoxic Agents on Adult Men	2134
Effects of Cytotoxic Agents on Adult Women	2137
Effects of Cytotoxic Agents on Children	2139
Gonadal Dysfunction after Cranial Irradiation	2139
Preservation of Fertility, Hormone Levels, and Sexual Function	2140
Pharmacologic Attempts at Preserving Fertility in Men	2143
Pharmacologic Attempts at Preserving Fertility in Women	2143
Fertility Preservation in Women with Cervical Cancer	2143
Genetic Concerns	2144

Acknowledgments	2145
134. Fatigue.....	2148
<i>Sandra A. Mitchell and Ann M. Berger</i>	
Introduction	2148
Definition, Risk Factors, and Mechanisms of Cancer-Related Fatigue	2148
Screening and Evaluation of the Patient with Cancer-Related Fatigue	2150
Interventions for Cancer-Related Fatigue	2150
Pharmacologic Interventions	2151
Nonpharmacologic Interventions	2152
Complementary and Integrative Therapies	2152
Summary	2153
135. Second Cancers.....	2155
<i>Chunkit Fung, Smita Bhatia, James M. Allan, Kevin C. Oeffinger, Andrea Ng, and Lois B. Travis</i>	
Introduction	2155
Carcinogenicity of Individual Treatment Modalities	2155
Genetic Susceptibility to Second Primary Cancers	2157
Risk of Second Malignancy in Patient with Selected Primary Cancers	2159
Pediatric Malignancies	2163
Comment	2169
136. Neurocognitive Effects	2174
<i>Paul D. Brown, Alissa M. Butts, Michael W. Parsons, and Jane H. Cerhan</i>	
Introduction	2174
Assessment of Cognitive Function	2174
Neurocognitive Effects of Central Nervous System Tumors and Treatment	2174
Neurocognitive Effects in Non-Central Nervous System Cancer	2176

Treatment of Cognitive Dysfunction	2178
Conclusion	2178
137. Cancer Survivorship.....	2180
<i>Wendy Landier, Michelle Shayne, Kevin C. Oeffinger, Smita Bhatia, and Louis S. Constine</i>	
Introduction	2180
Definition of Survivorship and Scope of the Problem	2180
Goals of Survivorship Health Care	2181
Care Plans	2183
Delivery of Follow-up Care and Best Practice Models	2184
Educational Considerations	2185
Enhancing Research	2185
Survivorship Advocacy	2185
Conclusion	2186
PART VI	
Palliative and Alternative Care	
SECTION 1. SUPPORTIVE CARE AND QUALITY OF LIFE	
138. Management of Cancer Pain.....	2190
<i>Thomas W. Leblanc and Arif H. Kamal</i>	
Introduction	2190
Epidemiology	2190
Definition of Pain	2191
Types of Pain	2191
Temporal Aspects of Pain	2191
Intensity of Pain	2192
Measurement Schemas	2192
Patient-Reported Outcome Measures	2192

Common Pain Syndromes	2193
Clinical Assessment of Pain	2193
Management of Cancer Pain	2195
Pharmacologic Management of Cancer Pain	2195
Adjuvant Drugs	2202
Adjuvants to Treat Side Effects	2205
Psychological Approaches	2205
Anesthetic and Neurosurgical Approaches	2205
Neuropharmacologic Approaches	2207
Neuroablative and Neurostimulatory Procedures for the Relief of Pain	2207
Trigger Point Injection and Acupuncture	2208
Physical Approaches	2208
Algorithm for Cancer Pain Management	2208
Future Directions	2208
Acknowledgments	2208
139. Nutrition Support	2212
<i>David A. August, Mihir M. Shah, and Maureen B. Huhmann</i>	
Background	2212
Causes of Malnutrition in Cancer Patients	2212
Cancer Cachexia Syndrome	2213
Nutrition Screening and Assessment	2214
Pharmacotherapy of Cancer-Associated Weight Loss and Malnutrition	2215
Nutrition Support of Cancer Patients	2215
140. Sexual Problems.....	2220
<i>Eric S. Zhou and Sharon L. Bober</i>	
Introduction	2220
Cancer in Men	2220

Cancers that Affect Men and Women	2221
Cancer in Women	2222
Cancer in Children and Young Adults	2224
Relevant Sociocultural Considerations	2225
Disruption of Intimacy and Relational Considerations	2225
Communication About Sexual Problems	2225
141. Psychological Issues	2229
<i>David Spiegel and Michelle B. Riba</i>	
Introduction	2229
Common Psychiatric Conditions	2229
Screening for Psychological Problems	2230
Coping	2230
Treatment Interventions	2231
Implications for Cancer Progression and Mortality	2233
Psychotropic Medication	2233
Conclusion	2236
142. Communicating News to the Cancer Patient	2238
<i>Eric J. Cassell</i>	
Introduction	2238
Preventing Illness	2238
Communication	2239
Explanations	2240
Uncomfortable Questions	2240
Information	2240
Meaning	2241
Cafeteria Explanations	2241

143. Specialized Care of the Terminally Ill	2242
<i>Robert S. Krouse and Arif H. Kamal</i>	

Introduction 2242

Early Specialist Palliative Care 2242

Communication 2242

Specific Problems in the Setting of Advanced Cancer 2242

Impending Death 2245

Conclusions 2246

144. Rehabilitation of the Cancer Patient	2248
---	------

Michael D. Stubblefield

Introduction 2248

The Rehabilitation Team 2249

Complications of Cancer and Its Treatment 2250

Neuromuscular Complications of Cancer and Cancer Treatment 2251

Musculoskeletal Complications of Cancer and Cancer Treatment 2257

Radiation Fibrosis Syndrome 2258

Head and Neck Cancer 2261

Lymphedema 2263

Rehabilitation Interventions 2264

SECTION 2. COMPLEMENTARY, ALTERNATIVE, AND INTEGRATIVE THERAPIES

145. Complementary, Alternative, and Integrative Therapies in Cancer Care	2269
---	------

Catherine E. Ulbricht, Oliver Grundmann, Eunji Michelle Ko, and Nikhil Sangave

Background 2269

Establishing an Integrative Oncology Approach with Patients 2269

Standardization and Quality 2271

Specific Complementary and Integrative Medicine Therapies 2272

Index 2285