

# Contents

## 1 Epidemiology of Bone and Soft Tissue Sarcomas

Logan G. Spector, Julie A. Ross,  
Rajaram Nagarajan

1.1	Descriptive Epidemiology of Bone Tumors . . . .	1
1.2	Worldwide Statistics . . . . .	1
1.3	North American Statistics . . . . .	3
1.4	Mortality and Survivorship . . . . .	4
1.5	Etiology of Bone Sarcomas . . . . .	5
1.6	Bone Sarcomas: Future Directions . . . . .	7
1.7	Epidemiology of Soft Tissue Sarcomas . . . . .	7
	References . . . . .	9

## 2 Pathologic and Molecular Techniques Used in the Diagnosis and Treatment Planning of Sarcomas

Timothy Triche, Deborah Schofield

2.1	Introduction . . . . .	13
2.2	Standard Histopathology . . . . .	14
	2.2.1 Light Microscopy . . . . .	14
	2.2.2 Immunohistochemistry . . . . .	15
	2.2.3 Electron Microscopy . . . . .	16
2.3	Cytogenetics . . . . .	16
	2.3.1 Classical Cytogenetic Analysis . . . . .	16
	2.3.2 In-Situ Hybridization . . . . .	18
	2.3.3 Spectral Karyotyping . . . . .	19
	2.3.4 Comparative Genomic Hybridization . . . .	20
2.4	Molecular Genetic Techniques . . . . .	20
	2.4.1 Introduction . . . . .	20
	2.4.2 PCR and Q-PCR . . . . .	20
	2.4.3 Microarrays . . . . .	23
	2.4.4 Proteomics . . . . .	27
	2.4.5 Conclusion . . . . .	30
	References . . . . .	31

## 3 Diagnostic Imaging of Pediatric Bone and Soft Tissue Sarcomas

Thomas D. Henry, Mary E. McCarville,  
Fredric A. Hoffer

3.1	Introduction . . . . .	35
3.2	Initial Evaluation of Bone and Soft Tissue Sarcomas . . . . .	35
3.3	Imaging Techniques for Evaluating the Primary Tumor . . . . .	37
3.4	Staging . . . . .	38
	3.4.1 Local Extent of the Tumor . . . . .	38
	3.4.2 Detection of Metastatic Disease . . . . .	40
3.5	Criteria for Evaluating Treatment Response . . .	41
3.6	Outcome Criteria . . . . .	43
3.7	Biopsy of the Primary Lesion . . . . .	43
3.8	Imaging Characteristics of Specific Tumors . . .	44
	3.8.1 Bone Sarcomas . . . . .	44
	3.8.1.1 Osteosarcoma . . . . .	44
	3.8.1.2 Chondrosarcoma . . . . .	48
	3.8.1.3 Ewing Sarcoma of Bone . . . . .	48
	3.8.2 Soft Tissue Sarcomas . . . . .	51
	3.8.2.1 Differentiating Benign from Malignant Soft Tissue Lesions . . . . .	51
	3.8.2.2 Soft Tissue Ewing Sarcoma Family of Tumors . . . . .	52
	3.8.2.3 Rhabdomyosarcoma . . . . .	54
	3.8.2.4 Non-rhabdomyosarcoma Soft Tissue Sarcomas . . . . .	61
	3.8.2.4.1 Synovial Sarcoma . . . . .	61
	3.8.2.4.2 Congenital Fibrosarcoma . . . . .	62
	3.8.2.4.3 Hemangiopericytoma . . . . .	63
	3.8.2.4.4 Malignant Peripheral Nerve Sheath Tumors (MPNST) . . . . .	65
3.9	Post-treatment Imaging Concerns . . . . .	66
3.10	Radiofrequency Ablation . . . . .	66
	References . . . . .	67

## 4 Local Control Issues in Pediatric Bone and Soft Tissue Sarcomas

John C. Breneman, David Rodeberg,  
Ruth F. Lavigne, Ken Brown, Eugene S. Wiener

4.1	Significance of Local Control in Pediatric Sarcomas . . . . .	71
4.2	Background to Local Control Modalities . . . . .	72
4.2.1	Patterns of Tumor Growth . . . . .	72
4.2.2	Surgery . . . . .	72
4.2.2.1	Biopsy Guidelines . . . . .	72
4.2.2.2	Surgical Margins . . . . .	72
4.2.3	Radiation Therapy . . . . .	73
4.2.3.1	Types of Radiation . . . . .	73
4.2.3.2	Techniques of Radiotherapy . . . . .	73
4.2.3.3	Treatment Morbidity . . . . .	74
4.2.4	Combined Surgery and Radiotherapy for Local Control . . . . .	74
4.2.5	Chemotherapy for Local Control . . . . .	75
4.3	Ewing's Sarcoma . . . . .	75
4.3.1	Surgery for Ewing's Sarcoma . . . . .	75
4.3.2	Radiation Therapy for Ewing's Sarcoma . . . . .	76
4.3.2.1	Radiotherapy Treatment Factors . . . . .	76
4.4	Rhabdomyosarcoma . . . . .	77
4.4.1	Surgery for Rhabdomyosarcoma . . . . .	77
4.4.2	Radiotherapy for Rhabdomyosarcoma . . . . .	78
4.4.3	Site Specific Approaches to Local Control . . . . .	79
4.4.3.1	Orbit and Head & Neck . . . . .	79
4.4.3.2	Genitourinary: Bladder/Prostate . . . . .	79
4.4.3.3	Vagina and Uterine Sites . . . . .	80
4.4.3.4	Paratestes . . . . .	80
4.4.3.5	Extremity . . . . .	80
4.4.3.6	Trunk . . . . .	81
4.5	Non-Rhabdomyosarcomatous Soft Tissue Sarcomas . . . . .	81
4.5.1	Surgery for Non-Rhabdo Soft Tissue Sarcomas . . . . .	81
4.5.2	Radiotherapy for Non-Rhabdo Soft Tissue Sarcomas . . . . .	82
4.6	Osteosarcoma . . . . .	83
4.6.1	Surgery for Osteosarcoma . . . . .	83
4.6.2	Radiotherapy for Osteosarcoma . . . . .	84
	References . . . . .	84

## 5 Drug Discovery in Pediatric Bone and Soft Tissue Sarcomas Using In Vivo Models

Jennifer K. Peterson, Peter J. Houghton

5.1	Introduction . . . . .	89
5.2	Pediatric Tumor Models . . . . .	90

5.3	General Criteria for Selecting Appropriate Models . . . . .	91
5.4	Expression Profiles . . . . .	91
5.5	Criteria for Selecting RMS Xenografts for Drug Evaluation . . . . .	92
5.5.1	In Vivo Models in Drug Discovery . . . . .	93
5.5.2	Models for Optimizing Therapy . . . . .	94
5.6	Combination Therapy . . . . .	95
5.7	Molecular Targeted Agents . . . . .	97
5.8	Combining Signal Transduction Inhibitors . . . . .	97
5.9	Future Directions . . . . .	99
	References . . . . .	100

## 6 Pediatric Rhabdomyosarcoma: Biology and Results of the North American Intergroup Rhabdomyosarcoma Trials

Alberto Pappo, Fred G. Barr,  
Suzanne L. Wolden

6.1	Epidemiology . . . . .	104
6.2	Pathology and Biology of Rhabdomyosarcoma . . . . .	105
6.2.1	Pathologic Classification of Rhabdomyosarcoma . . . . .	105
6.2.2	Chromosomal Translocations in Alveolar Rhabdomyosarcoma . . . . .	106
6.2.3	Allelic Loss of 11p15.5 in Embryonal Rhabdomyosarcoma . . . . .	108
6.2.4	Other Genetic Changes in Rhabdomyosarcoma . . . . .	108
6.3	Clinical Presentation and Evaluation of Extent of Disease . . . . .	110
6.3.1	Head and Neck Region . . . . .	110
6.3.2	Genitourinary Tumors . . . . .	110
6.3.3	Extremity Tumors . . . . .	110
6.3.4	Trunk . . . . .	110
6.3.5	Other Sites . . . . .	111
6.4	Staging . . . . .	111
6.5	Prognostic Factors . . . . .	114
6.6	Treatment . . . . .	114
6.7	Role of Local Therapies . . . . .	115
6.8	Multi-institutional Trials . . . . .	117
6.8.1	Clinical Group I . . . . .	117
6.8.2	Clinical Group II . . . . .	120
6.8.3	Clinical Group III . . . . .	120
6.8.4	Clinical Group IV . . . . .	121
6.9	Management of Specific Tumor Sites . . . . .	121
6.9.1	Parameningeal Tumors . . . . .	121
6.9.2	Orbital Tumors . . . . .	121
6.9.3	Head and Neck Non-Orbital, Non-Parameningeal Tumors . . . . .	122
6.9.4	Parotid Tumors . . . . .	122
6.9.5	Extremity Tumors . . . . .	123
6.9.6	Paratesticular Rhabdomyosarcoma . . . . .	123

6.9.7	Female Genital Tract Tumors . . . . .	123
6.9.8	Bladder and Prostate Rhabdomyosarcoma . . . . .	124
6.10	<b>Other Sites . . . . .</b>	125
6.10.1	Biliary Tract Tumors . . . . .	125
6.10.2	Perineal and Perianal Rhabdomyosarcoma . . . . .	125
6.10.3	Pelvic and Retroperitoneal Rhabdomyosarcoma . . . . .	125
6.11	<b>Acute and Long Term Effects of Therapy . . . . .</b>	125
6.12	<b>Future Directions . . . . .</b>	127
6.13	<b>Outcome and Therapy of Relapse . . . . .</b>	127
	<b>References . . . . .</b>	128

## 7 Non-Rhabdomyosarcoma Soft Tissue Sarcomas

Sheri L. Spunt, Suzanne L. Wolden,  
Deborah E. Schofield, Stephen X. Skapek

7.1	<b>Epidemiology/Pathogenesis . . . . .</b>	134
7.1.1	Incidence . . . . .	134
7.1.2	Risk Factors . . . . .	134
7.2	<b>Pathology/Molecular Pathology . . . . .</b>	135
7.2.1	Molecular Pathogenesis . . . . .	137
7.2.2	Synovial Sarcoma and the SYT/SSX Translocation . . . . .	139
7.2.3	Infantile Fibrosarcoma and ETV6-NTRK3 . . . . .	139
7.2.4	Rhabdoid Tumor and INI1 . . . . .	139
7.2.5	Inflammatory Myofibroblastic Tumor and ALK . . . . .	140
7.2.6	Gastrointestinal Stromal Tumors and the KIT Transferase . . . . .	140
7.2.7	Dermatofibrosarcoma Protuberans and PDGF . . . . .	140
7.3	<b>Histologic Classification . . . . .</b>	140
7.3.1	Synovial Sarcoma . . . . .	141
7.3.2	Malignant Peripheral Nerve Sheath Tumor . . . . .	142
7.3.3	Infantile Fibrosarcoma . . . . .	142
7.3.4	Adult Type Fibrosarcoma . . . . .	143
7.3.5	Rhabdoid Tumor . . . . .	143
7.3.6	Inflammatory Myofibroblastic Tumor . . . . .	144
7.3.7	Gastrointestinal Stromal Tumor . . . . .	144
7.3.8	Infantile Hemangiopericytoma . . . . .	145
7.3.9	Desmoplastic Small Round Cell Tumor . . . . .	145
7.3.10	Grading Systems . . . . .	146
7.4	<b>Clinical Presentation and Diagnosis . . . . .</b>	146
7.4.1	Presenting Features . . . . .	146
7.4.2	Differential Diagnosis . . . . .	146
7.4.3	The Diagnostic Biopsy . . . . .	147
7.4.4	Evaluation of Disease Extent . . . . .	147
7.5	<b>Prognostic Factors and Clinical Staging . . . . .</b>	148
7.5.1	Prognostic Factors . . . . .	148
7.5.2	Clinical Staging . . . . .	149

7.6	<b>Treatment . . . . .</b>	150
7.6.1	<b>Surgery . . . . .</b>	150
7.6.1.1	Surgical Management of the Primary Tumor . . . . .	150
7.6.1.2	Surgical Management of Metastases . . . . .	151
7.6.2	<b>Radiation Therapy . . . . .</b>	151
7.6.2.1	Radiation Planning . . . . .	152
7.6.2.2	Timing of Radiotherapy . . . . .	153
7.6.2.3	Brachytherapy . . . . .	153
7.6.2.4	New Technologies . . . . .	154
7.6.2.5	Acute Side Effects of Radiotherapy . . . . .	154
7.6.2.6	Long-Term Side Effects of Radiotherapy . . . . .	154
7.6.3	<b>Chemotherapy . . . . .</b>	155
7.6.3.1	Adjuvant Chemotherapy . . . . .	155
7.6.3.2	Neoadjuvant Chemotherapy . . . . .	156
7.6.3.3	Other Approaches to the Use of Standard Chemotherapy . . . . .	157
7.6.3.4	High-Dose Chemotherapy . . . . .	157
7.6.3.5	Novel Agents . . . . .	157
7.6.3.6	Late Effects of Chemotherapy . . . . .	158
7.7	<b>Current Problems and Future Challenges . . . . .</b>	158
	<b>References . . . . .</b>	158

## 8 Fibrous and Fibrohistiocytic Tumors

Diane Nam, Benjamin A. Alman

8.1	<b>Fibrous and Fibrohistiocytic Tumors . . . . .</b>	164
8.2	<b>Soft Tissue Fibrous Tumors . . . . .</b>	164
8.2.1	Epidemiology/Pathogenesis . . . . .	165
8.2.2	Pathology/Molecular Biology . . . . .	166
8.2.3	Clinical Presentation and Diagnosis . . . . .	166
8.2.4	Prognostic Factors and Clinical Staging . . . . .	167
8.2.4.1	Treatment of Fibrous Tumors . . . . .	168
8.2.4.2	Current Problems and Future Challenges . . . . .	168
8.3	<b>Fibrohistiocytic Tumors . . . . .</b>	169
8.4	<b>So-Called Fibrohistiocytic Tumors . . . . .</b>	169
8.4.1	<b>Histologic Classification . . . . .</b>	169
8.4.2	<b>Benign . . . . .</b>	170
8.4.2.1	Benign Fibrous Histiocytoma . . . . .	170
8.4.2.1.1	Epidemiology/Pathogenesis . . . . .	170
8.4.2.1.2	Pathology/Molecular Pathology . . . . .	171
8.4.2.1.3	Clinical Presentation and Diagnosis . . . . .	171
8.4.2.1.4	Prognostic Factors and Clinical Staging . . . . .	171
8.4.2.2	Giant Cell Tumor of Tendon Sheath and Diffuse-Type Giant Cell Tumor . . . . .	172
8.4.2.2.1	Epidemiology/Pathogenesis . . . . .	172
8.4.2.2.2	Pathology/Molecular Pathology . . . . .	172
8.4.2.2.3	Clinical Presentation and Diagnosis . . . . .	172
8.4.2.2.4	Prognostic Factors and Clinical Staging . . . . .	173

8.4.3	Intermediate . . . . .	173
8.4.3.1	Giant Cell Fibroblastoma and Dermatofibrosarcoma Protuberans . . . . .	173
8.4.3.1.1	Epidemiology/Pathogenesis . . . . .	173
8.4.3.1.2	Pathology/Molecular Pathology . . . . .	173
8.4.3.1.3	Clinical Presentation and Diagnosis . . . . .	174
8.4.3.1.4	Prognostic Factors and Clinical Staging . . . . .	174
8.4.3.2	Plexiform Fibrohistiocytic Tumor . . . . .	174
8.4.3.2.1	Epidemiology/Pathogenesis . . . . .	174
8.4.3.2.2	Pathology/Molecular Pathology . . . . .	174
8.4.3.2.3	Clinical Presentation and Diagnosis . . . . .	175
8.4.3.2.4	Prognostic Factors and Clinical Staging . . . . .	175
8.4.3.3	Giant Cell Tumor of Soft Tissue . . . . .	175
8.4.3.3.1	Epidemiology/Pathogenesis . . . . .	175
8.4.3.3.2	Pathology/Molecular Pathology . . . . .	175
8.4.3.3.3	Clinical Presentation and Diagnosis . . . . .	175
8.4.3.3.4	Prognostic Factors and Clinical Staging . . . . .	176
8.4.3.3.5	Treatment of Fibrohistiocytic Tumors . . . . .	176
8.5	Current Problems and Future Challenges . . . . .	176
	References . . . . .	177

## 9 Ewing Sarcoma Family of Tumors

Carlos Rodriguez-Galindo, Fariba Navid,  
Joseph Khoury, Matthew Krasin

<b>9.1</b>	<b>Introduction</b> . . . . .	181
<b>9.2</b>	<b>Epidemiology</b> . . . . .	182
<b>9.3</b>	<b>Pathogenesis</b> . . . . .	182
<b>9.4</b>	<b>Pathology</b> . . . . .	185
	9.4.1 Microscopic Features . . . . .	185
	9.4.2 Molecular Pathology . . . . .	186
<b>9.5</b>	<b>Clinical Features</b> . . . . .	188
	9.5.1 Extrasosseous ESFT . . . . .	189
	9.5.2 Laboratory and Radiologic Evaluation . . . . .	189
	9.5.3 Prognostic Factors . . . . .	190
<b>9.6</b>	<b>Treatment</b> . . . . .	192
	9.6.1 Treatment of Patients with Localized Disease . . . . .	192
	9.6.1.1 Four-Drug Regimens . . . . .	192
	9.6.1.2 Role of Ifosfamide and Etoposide . . . . .	192
	9.6.1.3 Increasing Dose Intensity . . . . .	195
	9.6.1.4 Current Studies . . . . .	199

9.6.2	Local Control in ESFT . . . . .	199
9.6.2.1	Surgical Therapy . . . . .	200
9.6.2.2	Surgery and Adjuvant Radiation Therapy . . . . .	201
9.6.2.3	Definitive Radiation Therapy . . . . .	202
9.6.2.4	Role of Systemic Chemotherapy in Local Control . . . . .	202
9.6.3	Treatment of Metastatic ESFT . . . . .	203
9.6.4	Myeloablative Therapy with Hematopoietic Stem Cell Rescue for Metastatic ESFT . . . . .	205
9.6.5	Second Malignancies . . . . .	207
9.6.6	Recurrent ESFT . . . . .	208
	<b>Future Developments . . . . .</b>	<b>208</b>
	<b>References . . . . .</b>	<b>211</b>

## 10 Osteosarcoma

Paul A. Meyers

10.1	Incidence . . . . .	219
10.2	Etiology/Pathogenesis . . . . .	219
10.3	Molecular Biology . . . . .	220
10.4	Pathology . . . . .	221
10.5	Clinical Presentation and Natural History . . . . .	222
10.6	Diagnostic Evaluation . . . . .	222
10.7	Biopsy . . . . .	223
10.8	Staging . . . . .	223
10.9	Prognostic Factors . . . . .	223
10.10	Treatment . . . . .	225
10.11	Surgery . . . . .	227
10.12	Radiation Therapy . . . . .	227
10.13	Recurrent Disease . . . . .	228
10.14	Future Directions . . . . .	228
	References . . . . .	228

**Subject Index** . . . . . 235



<http://www.springer.com/978-3-540-40843-7>

Pediatric Bone and Soft Tissue Sarcomas

Pappo, A.S. (Ed.)

2006, XIV, 240 p., Hardcover

ISBN: 978-3-540-40843-7