This is an abundantly illustrated resource for diagnosis of bone and soft tissue lesions—a particular challenge due to their rarity and complexity. In addition to carefully selected histologic photographs, this unique atlas enhances standard visual information with illustrations of imaging findings, cytology, and molecular and cytogenetic information. This vivid pictorial survey is arranged in a pattern-oriented approach based on the actual working method used in daily practice.

The authors are expert educators in surgical and cytopathology and experienced diagnosticians in the complexities of soft tissue and bone pathology. This richly illustrated and concise reference will be a practical and indispensable tool for general pathologists and pathologists in training, who are required to diagnose bone and soft tissue pathologies. It is also an excellent resource for physicians seeking a quick survey of sarcoma.

Key Features:

➤ Offers a practical, pattern-oriented diagnostic approach that mirrors the working method used in daily practice
➤ Augments histologic photographs with illustrations of imaging findings, cytology, and molecular and cytogenetic information
➤ Authored by recognized expert diagnosticians and teachers in the field
Atlas of Soft Tissue and Bone Pathology
Atlas of Soft Tissue and Bone Pathology

With Histologic, Cytologic, and Radiologic Correlations

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To my mentors, teachers, colleagues, and trainees.
To my husband Cliff, for his patience and support. (LD)

To my late grandmother, my parents, brothers and their families for their love,
To my husband for his enduring and loving support,
To my daughter Katie whom is my pride, joy, and secret inspiration. (MB)
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Preface

Why another tome on bone and soft tissue sarcoma? There are already a number of excellent and comprehensive works on this topic by numerous authors, some with multiple editions to their credit. The authors of this volume undertook the task of compiling this *Atlas of Soft Tissue and Bone Pathology* with the goal to present to potential readers a very unique type of work.

One challenge for the authors was to present this material in a manner that is simultaneously practical and logical. We have chosen to arrange this material in a more or less “pattern-based” scheme. This approach to diagnosing lesions of soft tissue and bone differs from the standard classification scheme in that it emphasizes morphologic features instead of a presumed tissue of origin. While this approach has its relative merits and drawbacks, we feel it is particularly well suited to diagnosis on small tissue samples. Those of us who have been in practice for a number of years have seen a dramatic decrease in the quantity of specimen available for examination. At the same time, we are being asked to provide more information to guide and facilitate appropriate treatment. In some instances, this may include neoadjuvant therapy that will hopefully obliterate the tumor before it is removed for final pathologic examination.

The authors of this book fully embrace the move to small needle biopsy specimens, both core biopsy and fine needle aspiration. Even on a quick perusal through this work, it will become obvious that we are enthusiastic about the role of fine needle aspiration in the diagnosis of sarcoma. Wherever possible we have tried to provide high quality examples of the representative cytologic features of many of the entities discussed and illustrated. We acknowledge that the diagnosis of sarcoma primarily by fine needle aspiration is controversial and practiced at only a handful of centers. Nevertheless, we feel that illustration of these findings in this volume is important for several reasons. Needle core biopsy now represents the first-line diagnostic procedure of choice in most sarcoma centers. When cores are obtained under image guidance, there are frequently requests for “rapid on site evaluation” (ROSE) for an assortment of reasons. Many will use ROSE as a tool to ensure that any given specimen is “adequate” and representative of the lesion. But immediate study of the cytologic findings also represents an additional opportunity to identify features that may be helpful in formulating a final diagnosis. In addition, a cytologic “snapshot” of the tumor can help facilitate an appropriate “triage” of material for appropriate ancillary study. The latter is crucial, as the “do more with less” challenge requires that tissue be utilized in the most efficient manner possible.

Readers of this *Atlas* will also note that there are a number of radiographic illustrations. These were included for several reasons. First, imaging studies provide extremely valuable information about the nature of any given tumor. While pathologists are not expected to be experts at interpreting various imaging modalities, it is essential that those working in the field of “sarcoma” have some knowledge of the basic features of tumors on imaging. In addition, we feel that it is important that pathologists be active participants in the multidisciplinary approach to sarcoma diagnosis and treatment. Examination of imaging, commonly in a tumor board setting, is becoming a routine part of the day for those of us who attempt to become proficient in the diagnosis of sarcoma.

In summary, we have attempted to provide a fairly comprehensive yet concise guide to most of the more common soft tissue and bone lesions. We have purposely strived to keep the text at a minimum but have raided our collective image files and exhibited these with abandon. We sincerely hope that the users of this *Atlas* will find this is a valuable “scope side” reference source.

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INTRODUCTION
Sarcoma” is a term derived from a Greek word, which translates as “fleshy growth.” Sarcomas are defined as deriving from cells of mesodermal origin including fat, connective tissues, tendon, bone, and cartilage. Thus the term “sarcoma” is often used to describe tumors of both bone and soft tissue. The incidence of malignant bone and soft tissue lesions in the United States is approximately 14,000 cases per year. As such, sarcomas represent less than 1% of all cases of cancer in any given year. It is important to remember that benign lesions of bone and soft tissue outnumber malignant sarcomas by about 10 to 1.

Sarcomas of bone and soft tissue are extremely diverse. To date, there are almost 100 different types of soft tissue neoplasms that have been described and incorporated into the World Health Organization (WHO) scheme of tumor classification. Many of these lesions represent exceedingly rare entities that have only been recently described or documented, often by large referral centers. Alternatively, many of these lesions are so common (lipomas, superficial fibromatoses) as to be easily overlooked or dismissed as lesions of no consequence.

The etiology of sarcoma is unknown. There are clearly some features that place an individual at an increased risk of developing sarcoma. These include radiation exposure as well as some specific oncogenic viral infections and immunodeficient states. In addition, there are some particularly vulnerable individuals, those with either inherited or acquired genetic defects (Table 1.1.1).

### CLASSIFICATION AND NOMENCLATURE

The systemic classification of sarcomas into diagnostically recognizable different subtypes began in the early part of the 20th century. The original classification schemes were based on the presumed tissue of origin of the sarcoma or the type of histologic differentiation. Hence the use of the terms “liposarcoma” for lesions of adipocytic origin and the terms “leiomyosarcoma” and “rhabdomyosarcoma” to signify origin from smooth and striated muscle, respectively. Minor alterations to the classification paradigm were made with the widespread adoption of immunohistochemical techniques. In addition, there have been some changes in classification based on current molecular and cytogenetic information. No doubt, the “traditional” scheme will continue to evolve as more information becomes available. The current iteration of the traditional classification scheme is outlined in Table 1.1.2.

The traditional classification system remains largely intact and persists as the primary means of identifying and subclassifying lesions of soft tissue and bone. Although this system remains the acknowledged standard, it is not without some shortcomings. For instance, there are a large number of entities for which origin is still unclear at this point. The latter would include an assortment of neoplasms such as clear cell sarcoma, alveolar soft part sarcoma, and angiomatoid fibrous histiocytoma. Under the current scheme, these diverse neoplasms are simply lumped into an “other” category. In addition, many of the high-grade pleomorphic sarcomas (pleomorphic rhabdomyosarcoma, liposarcomas, etc.) resemble each other more than their namesake tissues of origin. And it goes without saying that there are still many true misnomers that have unfortunately been codified into the current classification and nomenclature scheme. One of the most obvious of these is synovial sarcoma.

As diagnosis of mesenchymal tumors has moved from an open biopsy to a smaller biopsy type (either cutting needle core or fine needle biopsy), there has been a parallel evolution of an alternative classification scheme. The so-called “pattern-based” approach was first largely used by aspiration cytopathologists in attempts to classify neoplasms based on the most prevalent morphologic feature. As such, categories such as “spindle cell” or “myxoid” or “epithelioid” terms emerged. This type of classification system represented a practical attempt to define the tumor type on the most minimal of characteristics. Early proponents of the cytologic descriptions and characterization of bone and soft tissue neoplasms were quick to broaden the pattern recognition approach and legitimate its use in the diagnostic setting. Current defined categories for lesions of soft tissue include tumors with adipose stroma, myxoid lesions, spindle cell lesions, small round blue cell tumors, pleomorphic tumors, and others (Figures 1.1.1–1.1.6). Similar categories exist for a “pattern-based” approach to the diagnosis of bone tumors, but these categories tend to be based on the predominant stromal feature (osteoid vs. cartilage) and as such, extensively overlap the traditional classification scheme (Figures 1.1.7–1.1.12). This approach has also been adopted by surgical pathologists who find that when working with small core biopsies, this type of alternative classification model can be extremely useful.

The pattern-based approach, although very practical, is not without problems either. Many neoplasms, again synovial sarcoma is just one, do not fit neatly into any given pattern as they often are both “spindled” and “epithelioid” at the same time. Likewise, many lesions, plexiform fibrohistiocytic tumors, for instance, have architectural features that define the lesion, but do not fit easily into any one of the simplistic categories. And lastly, categorization of lesions by
a pattern-based approach will break up many classes of related tumors that may be best compared to one another. The different subtypes of liposarcoma, for example, all have recognizable lipogenic differentiation, but will be subcategorized into “spindled” or “myxoid” or “pleomorphic” categories under a pure pattern recognition approach.

Recognizing the relative merits and faults of each of these two major classification strategies, the authors of this atlas have elected not to be purists, but to present this material in a “hybrid” format with an emphasis on pattern recognition (Table 1.1.3). Thus, adipocytic, osseous, and cartilaginous tumors remain largely intact as groups instead of split into various categories. But the broad categories of “myxoid,” “small round blue cell tumors,” and “spindle tumors” are presented under a pattern-based approach.
1: INTRODUCTION

FIGURE 1.1.1 Adipose tissue is easily recognized in aspirates and small biopsy specimens.

FIGURE 1.1.2 Extracellular matrix material is a unifying characteristic of a large group of soft tissue lesions.

FIGURE 1.1.3 Spindle cell lesions are another major category of soft tissue tumors in a pattern-based paradigm.

FIGURE 1.1.4 There are numerous epithelioid soft tissue lesions that can mimic both melanoma and poorly differentiated carcinoma.

FIGURE 1.1.5 Small round blue cell tumors are a diagnostic challenge on both traditional biopsy samples and needle aspiration.

FIGURE 1.1.6 Pleomorphic forms of sarcoma are characterized by marked diversity in cell size and shape.
FIGURE 1.1.12 Cystic lesions of bone are often difficult to diagnose by small biopsy specimens. In this example, a cell block prepared from an aspirate of an aneurysmal bone cyst contained fragments of the cyst wall.
### TABLE 1.1.1 Genetic Syndromes Associated With a Disposition to Develop Bone and Soft Tissue Neoplasms

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Hereditary Pattern</th>
<th>Chromosome</th>
<th>Genetic/Molecular Aberration</th>
<th>Bone and Soft Tissue Tumor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Familial adenomatous polyposis 1</td>
<td>AD</td>
<td>5q21</td>
<td>APC mutation</td>
<td>Desmoid tumor, Gardner fibroma, craniofacial osteoma</td>
</tr>
<tr>
<td>Li-Fraumeni 1</td>
<td>AD</td>
<td>17q13</td>
<td>TP53 mutation</td>
<td>Osteosarcoma, rhabdomyosarcoma</td>
</tr>
<tr>
<td>Li-Fraumeni 2</td>
<td>Sporadic or AD</td>
<td>22q12</td>
<td>CHEK2</td>
<td>Osteosarcoma, rhabdomyosarcoma, soft tissue sarcoma</td>
</tr>
<tr>
<td>McCune-Albright</td>
<td>Sporadic</td>
<td>20q13</td>
<td>Mosaicism for a mutation in the GNAS1 gene</td>
<td>Fibrous dysplasia</td>
</tr>
<tr>
<td>Mazabraud</td>
<td>Sporadic</td>
<td>20q13</td>
<td>Activating GNAS1 mutation</td>
<td>Fibrous dysplasia, myxoma</td>
</tr>
<tr>
<td>Maffucci</td>
<td>Sporadic</td>
<td>3p21-22</td>
<td>PTH1R mutations</td>
<td>Enchondromatosis, hemangioma, chondrosarcoma, angiosarcoma</td>
</tr>
<tr>
<td>Neurofibromatosis, type 1</td>
<td>Sporadic or AD</td>
<td>17q11.2</td>
<td>Neurofibromin (p21/ras pathway)</td>
<td>Neurofibroma</td>
</tr>
<tr>
<td>Ollier disease</td>
<td>Sporadic</td>
<td>3p21-22</td>
<td>PTH1R mutations</td>
<td>Enchondromatosis, chondrosarcoma</td>
</tr>
<tr>
<td>Tuberous sclerosis 1</td>
<td>AD</td>
<td>9q34</td>
<td>TSC1 (hamartin)</td>
<td>Fibroma, cardiac rhabdomyoma, angiomyolipoma, chordoma</td>
</tr>
<tr>
<td>Tuberous sclerosis 2</td>
<td>AD</td>
<td>16p13</td>
<td>TSC2 (tuberin)</td>
<td>Fibroma, cardiac rhabdomyoma, angiomyolipoma, chordoma, PEComa</td>
</tr>
</tbody>
</table>

**Abbreviation:** AD, autosomal dominant.

### TABLE 1.1.2 Traditional Classification of Tumors of Primary Soft Tissue and Bone Lesions

Major categories of soft tissue tumors

1. Adipocytic tumors
2. Fibroblastic/myofibroblastic tumors
3. Fibrohistiocytic tumors
4. Smooth muscle tumors
5. Pericytic (perivascular) tumors
6. Skeletal muscle tumors
7. Vascular tumors
8. Chondro-osseous tumors
9. Gastrointestinal stromal tumors
10. Nerve sheath tumors
11. Tumors of uncertain differentiation
12. Undifferentiated/unclassified sarcomas

Major categories of bone tumors

1. Chondrogenic tumors
2. Osteogenic tumors
3. Fibrogenic tumors
4. Fibrohistiocytic tumors
5. Ewing sarcoma
6. Hematopoietic neoplasms
7. Osteoclastic giant cell-rich tumors
8. Notochordal tumors
9. Vascular tumors
10. Myogenic, lipogenic, and epithelial tumors
11. Tumors of undefined neoplastic nature
12. Undifferentiated high-grade pleomorphic sarcoma

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### TABLE 1.1.3  A Largely “Pattern-Based” Approach to Diagnosis of Primary Soft Tissue and Bone Tumors

<table>
<thead>
<tr>
<th>Soft tissue lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Lesions with adipose differentiation</td>
</tr>
<tr>
<td>2. Lesions with myxoid stroma</td>
</tr>
<tr>
<td>3. Spindle cell neoplasms(^a)</td>
</tr>
<tr>
<td>4. Epithelioid soft tissue tumors</td>
</tr>
<tr>
<td>5. Small round cell tumors</td>
</tr>
<tr>
<td>6. Giant cell-rich tumors</td>
</tr>
<tr>
<td>7. Soft tissue tumors with prominent inflammation</td>
</tr>
<tr>
<td>8. Vascular lesions(^b)</td>
</tr>
<tr>
<td>9. Pleomorphic soft tissue tumors</td>
</tr>
<tr>
<td>10. Soft tissue tumors with extensive cartilaginous or osseous matrix</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Primary lesions of bone</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Osseous lesions</td>
</tr>
<tr>
<td>2. Cartilaginous lesions</td>
</tr>
<tr>
<td>3. Giant cell-rich lesions</td>
</tr>
<tr>
<td>4. Spindle cell lesions</td>
</tr>
<tr>
<td>5. Small round blue cell tumors</td>
</tr>
<tr>
<td>6. Cystic lesions</td>
</tr>
</tbody>
</table>

\(^a\) The spindle cell category contains a large number of entities. There are many different strategies for subclassification for this group. Some authors have chosen to divide them into “superficial” versus “deep,” or “pediatric” versus “adult.” In this work, the “spindle cell category” has been separated into “benign/low-grade” and “high-grade” lesions. The authors recognize this distinction is somewhat artificial, and many spindle cell tumors (solitary fibrous tumor, low-grade leiomyosarcoma, low-grade fibroxoid sarcoma) are difficult to classify in this simplistic scheme.

\(^b\) “Vascular lesions” is technically not a category under a true “pattern-based” approach. However, small biopsy specimens are often characterized by abundant blood and rare stromal fragments. The authors have chosen to describe and illustrate these lesions together under the traditional histologic category of vascular lesions.