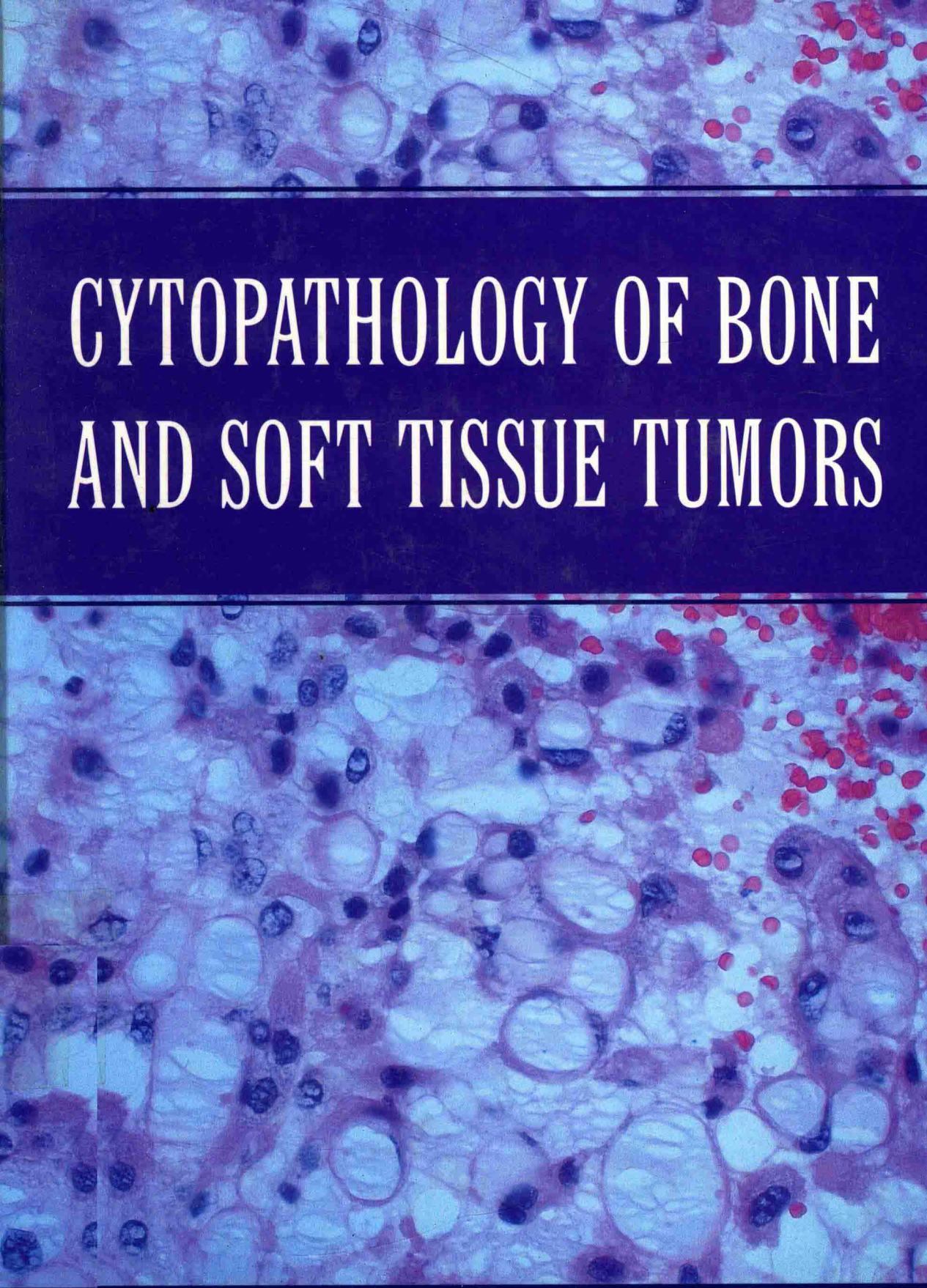

CYTOPATHOLOGY OF BONE AND SOFT TISSUE TUMORS

LESTER J. LAYFIELD

Cytopathology of Bone and Soft Tissue Tumors

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To the surgical orthopedic oncologists at Duke University Medical Center, and
the University of California Medical Center at Los Angeles,
and especially to John M. Harrelson, M.D.,
Sean Scully, M.D.,
Jeffrey Eckhardt, M.D.,
Frederick Eilber, M.D.,
and Joseph M. Mirra, M.D.

PREFACE

Fine-needle aspiration (FNA) is only now gaining acceptance as a primary diagnostic modality for the study of musculoskeletal lesions. Several factors have been responsible for the delayed acceptance of the technique for the diagnosis of these tumors. These factors include FNA's limited ability to subtype neoplasms and grade sarcomas accurately, the unfamiliarity of many pathologists and cytopathologists with the cytomorphologic appearance of these relatively rare lesions, the cytomorphologic overlap between benign and malignant lesions in certain categories of spindle cell proliferations, and the relatively high insufficiency rate of the technique. Recent developments have reduced the importance of some of these issues.

Current therapeutic protocols have deemphasized the need for precise subtyping of soft tissue neoplasms and require only separation into low- and high-grade neoplasms. This simplification of diagnostic requirements for effective therapy allows wider usage of FNA for the investigation of musculoskeletal lesions. This text atlas has been written to furnish the practicing pathologist with a single source describing and illustrating the cytomorphologic appearance of the majority of musculoskeletal lesions. For those rare lesions for which illustrations were not available, descriptions and references to published descriptions are supplied. Every attempt has been made to make the atlas as encyclopedic as possible. While a number of textbooks contain sections on the FNA cytology of musculoskeletal lesions, descriptions and illustrations have been limited to the more common proliferations and the most common presentations of these entities. Few of these textbooks have attempted an encyclopedic description of the cytologic features of musculoskeletal tumors.

While FNA may not be chosen as the preferred diagnostic technique for the study of musculoskeletal tumors by many clinicians and pathologists, these neoplasms may be inadvertently aspirated in the workup of suspected metastatic disease. Hence, knowledge of the cytologic appearance of these tumors is helpful in separating them from metastatic deposits. Once a mesenchymal lesion is aspirated, as specific a cytologic diagnosis as possible should be given. While such a cytologic diagnosis may not be sufficient for definitive therapy, it does guide the clinician and the pathologist in selecting future diagnostic studies.

I have used a histocytologic correlative approach for two reasons. The first is to provide a histopathologic background to serve

as a basis for understanding the cytologic features present in smear specimens. Secondly, many cytopathologists obtain cell block or mini-core biopsy specimens at the time of FNA. These mini-core biopsy specimens are interpreted histologically but are an important component in the final FNA diagnosis of many musculoskeletal specimens. Side-by-side publication of histologic sections and cytologic smear preparations should aid the reader in using both specimen types to optimally establish a final diagnosis.

I believe that accurate cytologic diagnosis is best achieved by using air-dried preparations, Papanicolaou-stained smears, and hemotoxylin and eosin (H&E)–stained material. However, in my experience, Romanowsky-stained material appears to have major advantages over the other methods since it best demonstrates stromal substances. It is also the optimal method for analyzing hematopathologic material. Hence, I have illustrated the majority of the material in air-dried (Romanowsky-stained) preparations. Because many pathologists are most comfortable with the appearance of musculoskeletal lesions in H&E-stained sections, I have illustrated some lesions with H&E-stained material to facilitate correlation.

It is my belief that the judicious use of FNA for the diagnosis of musculoskeletal lesions can significantly improve the diagnosis and management of these lesions. The FNA technique can substantially decrease patient morbidity, lessen complications secondary to larger biopsy techniques, shorten the time required for diagnosis, and, finally, reduce the cost of diagnosis. While cytologic diagnosis of musculoskeletal lesions may not be as accurate as core biopsy in the subtyping of these neoplasms, the above advantages over histologic diagnosis encourage its utilization as the initial diagnostic technique. It is hoped that the present text atlas will facilitate the cytologic diagnosis of these neoplasms by the general pathology community.

Salt Lake City, Utah L.J.L.

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CYTOPATHOLOGY OF BONE AND SOFT TISSUE TUMORS

1

INTRODUCTION

Fine-needle aspiration (FNA) has been used for the diagnosis of musculoskeletal neoplasms since the time of its early descriptions by Martin and Ellis.[1,2] Despite the long history of FNA for the diagnosis of musculoskeletal lesions, it has been used relatively infrequently as a primary diagnostic technique for tumors arising in bone and soft tissues. Potential explanations include the relative unfamiliarity of cytopathologists with lesions occurring at these locations, the relative rarity of neoplasms arising primarily within the musculoskeletal system, the difficulty experienced by many pathologists in the histologic diagnosis of musculoskeletal tumors, and the relatively poor ability of FNA to subtype musculoskeletal lesions. Additionally, many clinicians believe that FNA is unable to supply sufficient tissue to perform ancillary studies including cytogenetic and molecular diagnostic studies. Despite these concerns, there are many compelling reasons for pathologists to be familiar with the cytologic appearance of lesions arising primarily within the musculoskeletal system.

Because FNA is frequently used for the investigation of suspected metastatic disease to subcutaneous soft tissue and skeletal sites, primary neoplasms and reactive processes arising within the musculoskeletal system may be inadvertently sampled by FNA during the workup of patients with known epithelial malignancies. Hence, familiarity with the range of cytopathologic features seen in primary musculoskeletal lesions is important for the diagnosis and/or exclusion of metastatic disease involving the musculoskeletal system.

Secondly, because FNA is a rapid diagnostic technique with limited patient morbidity, it may be preferred for the rapid diagnosis of superficial soft tissue lesions. This, combined with its relatively low cost, makes it an important alternative to more traditional biopsy techniques in the rapid workup of palpable tumors involving the musculoskeletal system. Finally, many lesions of soft tissues and bone occur in areas difficult to biopsy with traditional techniques. For these reasons, the relative merits and disadvantages of FNA in comparison to other biopsy techniques are discussed below.

COMPARISON OF FNA TO OTHER BIOPSY METHODS

Biopsy and prebiopsy staging studies are critical to the treatment outcome of aggressive benign and malignant neoplasms of the

musculoskeletal system.[3] The biopsy of a musculoskeletal lesion must be carefully planned, taking into consideration the lesion's site, radiographic features, patient age, patient health status, and presumptive diagnosis. Based on these prebiopsy data, the biopsy technique, approach, and arrangement for specialized pathologic studies (when needed) can be selected. Traditionally, open biopsy has been considered necessary before definitive surgery for a suspected malignancy of the musculoskeletal system can be performed. The purpose of the biopsy is to determine the histologic type and grade of the malignancy. With these two pieces of information, a therapeutic management plan, which may include radiation therapy or chemotherapy, can be formulated preoperatively. The performance of open biopsy is, however, not without significant hazards. Mankin et al.[4] demonstrated that major errors in biopsy diagnosis occurred in 17% of cases, and an additional 10% of biopsies yielded either nonrepresentative or technically poor specimens. Seventeen percent of biopsies were associated with problems in the skin, soft tissue, or bone of the biopsy wounds, and the optimal treatment plan had to be altered as a result of problems related to the biopsy in fully 18% of patients.[4] Moreover, open biopsy is invariably associated with some degree of trauma and bleeding into the tumor bed, potentially complicating subsequent surgical intervention.[4] With these issues in mind, surgeons and pathologists have sought alternative, minimally invasive biopsy techniques for the diagnosis of musculoskeletal lesions. Fine-needle aspiration and core biopsy are two techniques that minimize patient morbidity and disruption of the tumor and the surrounding tumor bed. However, although they reduce the hazards of the biopsy technique itself, these methods are unfortunately associated with some diminution of diagnostic accuracy. In the case of FNA, precise histologic typing is considerably less accurate than with open biopsy. In light of these constraints associated with the various biopsy methods, it is important to reevaluate the amount and type of information a surgeon requires from biopsy of a musculoskeletal lesion to plan optimal therapy. Because therapeutic protocols and the value of radiographic investigation differ between skeletal and soft tissue neoplasms, the utility of FNA will be discussed separately for these two tissue types.

BONE LESIONS

Radiographic evaluation of bone lesions yields abundant diagnostically useful information in the majority of cases. In many instances, the radiologist limits the diagnostic options to one or two entities. This greatly simplifies subsequent pathologic evaluation of biopsy material. In most cases, a pathologist should not attempt pathologic interpretation of bone specimens without knowledge of the radiologic differential diagnosis.[5] In the majority of instances, the orthopedic surgeon's requirements for the diagnosis are relatively limited. First, the surgeon needs to know if the lesion is benign or malignant. Once the presence of a malignancy is established, categorization of the neoplasm into a small cell or non–small cell malignancy is necessary. Therapeutic regiments differ significantly between those used for treatment of small round cell malignancies (Ewing's sarcoma) and those used for non–small cell sarcomas of bone. Once these two diagnostic hurdles have been passed, specific histologic typing of the neoplasm should be attempted. Any analysis of the utility of FNA for the diagnosis of bone lesions should be carried out in this background and should take into account the following: (*1*) diagnostic accuracy and limitations of other biopsy techniques; (*2*) diagnostic accuracy of FNA; (*3*) hazards and complications of FNA in the skeletal system; (*4*) clinical impact and utility of cytologic diagnosis; (*5*) patient acceptance and morbidity inherent in FNA; (*6*) speed of diagnosis by FNA; and (*7*) cost efficiency in relationship to other biopsy techniques.

As stated above, open biopsy is an imperfect diagnostic technique. In a study of 220 patients undergoing biopsy of bone lesions, Mankin et al.[4] documented significant diagnostic errors in 17% of biopsies. These errors were considered major in 15% of cases. This study looked at both open biopsy and cutting needle biopsy but did not break down the error rate by biopsy technique. The authors, however, stated that needle biopsies were as accurate as open biopsy in

their series. Ayala and Zoronosa reported a study of core needle biopsies in which a 78.6% accuracy rate was achieved in separating benign from malignant lesions.[6] DeSantos et al.[7] reported an 85% accuracy rate in separating benign from malignant lesions by core needle biopsy. Evaluation of the diagnostic utility of FNA must compare its published diagnostic accuracy rates with those achieved by open or cutting needle biopsy under similar circumstances rather than evaluating FNA by comparison to an arbitrary standard of 100% accuracy. Published diagnostic accuracy rates for the separation of benign from malignant lesions by FNA cytologic evaluation have varied from 54%[8] to 100%.[9] The majority of reported series have an accuracy rate of between 70% and 90% for the cytologic separation of benign from malignant primary lesions of bone.[10–14] In the majority of these studies, the reason for failure to obtain the appropriate diagnosis was insuffient tissue. Fibro-osseous lesions were particularly difficult to diagnose accurately.[13] In one study, fully 29% of aspirates were insufficient for diagnosis.[15] In this study, 10% of these aspirates resulted in an incorrect diagnosis, but only 30% of this group (3% of the total) resulted in a clinically significant error. When adequate material was obtained, the diagnostic accuracy of FNA in separating benign from malignant lesions was 86%.[15] Despite considerable variability in reported diagnostic accuracy rates for FNA in the literature, it appears that the technique has an approximately 85% accuracy rate when performed at centers with expertise in musculoskeletal pathology. The highest reported accuracy rates in the separation of benign from malignant lesions of bone are those obtained by authors reporting the largest number of cases.[10,11]

From the reported cytologic studies and that of Mankin et al.,[4] it would appear that the diagnostic accuracies of open biopsy, cutting needle biopsy, and FNA are relatively similar for the separation of benign from malignant neoplasms of bone. Of equal importance is a comparison of untoward affects suffered by the patient due to an inaccurate biopsy diagnosis. In a study by Layfield et al.,[15] only 3% of all FNAs performed on bone lesions resulted in an erroneous diagnosis that had a significant negative impact on clinical management. This compares favorably with the 18% rate of major diagnostic errors reported by Mankin et al.[4] for open and cutting needle biopsies.

Another concern in regard to FNA is its relatively high insufficiency rates, which have clustered around 30%–35%.[15,16] While these rates of insufficiency are considerably higher than the 10% rate reported by Mankin et al.,[4] it should be borne in mind that FNA is a simple, rapid technique associated with little patient morbidity. It can be easily repeated or followed by a biopsy technique yielding a larger size sample without undue financial burden to the patient.

Fine-needle aspiration of bone lesions appears to be relatively free of significant hazards. While no published study has specifically investigated the hazards and complications of FNA in the musculoskeletal system, its use at other sites (liver, lung, breast) is associated with very low rates of complication.[17–19] In my experience with over 200 FNAs of primary bone lesions, only a single localized hematoma has been documented, and no needle tract implantations of tumor have been recognized. Rare cases of needle tract implantation have been associated with sarcomas,[20] but their occurrence with thin needles appears to be very rare.[21] These findings are in contrast with those of Mankin et al.,[4] who documented "problems related to biopsy" in 18% of their study population.

While cost should not have a sizable impact on the biopsy technique chosen, FNA is associated with significant cost containment advantages (Table 1–1). At my practice location, a palpable FNA costs approximately $200, while an image-guided FNA costs approximately $1000. The charge for an open biopsy is over $6000. Hence, FNA cytology, even with a 30% repeat rate, allows substantial monetary savings.

SOFT TISSUE LESIONS

Like biopsy of the skeletal system, biopsy of soft tissue lesions is performed to obtain a histopathologic diagnosis and to determine the grade of the malignancy. The initial therapy for most soft tissue sarcomas is primarily surgical, and it is necessary to know the precise histopathologic type and grade only if this information is important in selecting the

Table 1–1. Cost Comparison FNAs versus Open Biopsy

FNA Cost	*Open Biopsy Cost*	*Savings*
FNA of palpable lesions $200	$6200	$6000
Palpable FNA including 30% repeat $260	$6200	$5940
Image-guided FNA $1000	$6200	$5200
Image-guided FNA with 30% repeat $1300	$6200	$4900
FNA if 30% repeat is followed by open biopsy $2600	$6200	$3600
Image-guided FNA if 30% repeat is followed by open biopsy $2860	$6200	$3340

surgical procedure to be performed.[22] At some treatment centers,[22] a diagnosis of sarcoma suffices for adequate treatment of most adult patients with soft tissue tumors, and the operative approach is not altered once the lesion is know to be a sarcoma. In these cases, simple separation of a soft tissue lesion into a benign or malignant category by FNA suffices. At other centers, treatment options for different soft tissue sarcomas vary, depending on the grade and size of the tumor. At the University of Utah, soft tissue sarcomas are treated according to a protocol based on stage, tumor size, and grade (Fig. 1–1). All sarcomas less than 5 cm in size undergo initial wide resection, with further therapy dictated by margin status and other elements of the histopathologic evaluation. Sarcomas more than 5 cm but of low grade histologically are treated similarly. Moderately differentiated and poorly differentiated sarcomas more than 5 cm in size receive preoperative neoadjuvant chemotherapy followed by surgical resection. Hence, under even this more complicated therapeutic protocol, precise histopathologic categorization is not necessary. The cytopathologist merely needs to decide whether a soft tissue lesion is benign or malignant. If it is malignant, the sarcoma should be graded according to a three-category scheme.[23] Thus, evaluation of the utility of FNA for the diagnosis of soft tissue lesions requires an analysis of the technique's accuracy in the separation of benign and malignant lesions and its accuracy in grading soft tissue sarcomas.

In a review of a 10-year experience at an orthopedic oncology center, Åkerman et

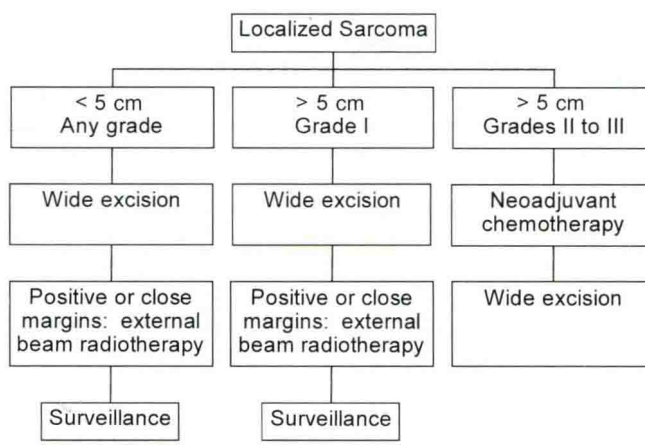

Figure 1–1. Adult soft tissue sarcoma treatment algorithm used at the University of Utah.