



## EXHIBIT SELECTION

# Current Concepts in the Biopsy of Musculoskeletal Tumors

## AAOS Exhibit Selection

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**Background:** A musculoskeletal tumor biopsy can involve fine needle aspiration, core needle biopsy, or incisional biopsy. Controversy regarding the diagnostic yield of these biopsy techniques continues. The purpose of this article is to summarize the current concepts in the biopsy of musculoskeletal tumors.

**Methods:** We performed a literature review of clinical articles reporting on the biopsy of bone and soft-tissue primary tumors. Clinical articles were excluded on the basis on abstract content if they represented case reports, review or opinion articles, or technique descriptions. Eighteen of the thirty-nine articles that remained were excluded because the results did not indicate the diagnostic accuracy of the various biopsy techniques. Thus, twenty-one articles with diagnostic data on the biopsy of bone and soft-tissue tumors were included in this review.

**Results:** Core needle biopsy appeared to be more accurate than fine needle aspiration, and incisional biopsy appeared to be more accurate than both of these techniques, but the differences did not reach significance. Incisional biopsy was more expensive than the percutaneous biopsy methods. In deep musculoskeletal tumors, incorporation of ultrasonography or computed tomography for guidance is easy and safe and can be useful for increasing the accuracy of the biopsy. Advantages of a percutaneous technique compared with an incisional one are the low risk of contamination and the minimally invasive nature. Certain anatomic locations and histologic types were associated with diagnostic difficulty. Vertebral tumors had the lowest diagnostic accuracy regardless of the biopsy technique. Myxoid, infection, and round cell histologies were associated with the lowest diagnostic accuracy.

**Conclusions:** The current literature has not clarified the optimal biopsy technique for the diagnosis of bone and soft-tissue tumors. However, core needle biopsy is usually preferable to incisional biopsy because of the low risk of contamination and the low cost. In addition, the use of imaging guidance increases the diagnostic accuracy of musculoskeletal biopsies and reduces the risk of complications. If the result of a percutaneous biopsy is nondiagnostic, a small incisional biopsy should be performed.

**Level of Evidence:** Diagnostic Level IV. See Instructions for Authors for a complete description of levels of evidence.

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In the management of bone and soft-tissue tumors, the use of a combination of clinical, radiographic, and histologic data to reach an accurate diagnosis and thus optimize treatment and outcomes is critical. On occasion, the diagnosis can be made on the basis of a carefully obtained history, physical examination, and images alone. However, the ultimate diagnosis usually depends on histologic analysis by an experienced pathologist. Biopsy is a very important and complex aspect of the staging process<sup>1</sup>. It must be performed carefully so as not to adversely affect the outcome<sup>2</sup>. Various biopsy techniques—fine needle aspiration, core needle (trocar) biopsy, and incisional (open) biopsy—are suitable. Although incisional biopsy is still considered the gold standard, recent literature suggests that percutaneous biopsy techniques (fine needle aspiration and core needle biopsy) yield similar results<sup>3</sup>. The aim of the present study was to review the literature and analyze the diagnostic accuracy of biopsy techniques for musculoskeletal tumors. After evaluating the current liter-

ature, we propose guidelines for biopsy techniques for bone and soft-tissue tumors (Fig. 1, Video 1 [online]).

### Materials and Methods

We used PubMed to perform a search for clinical studies published from 1993 to 2013 that involved the biopsy of bone and soft-tissue primary tumors. This search resulted in the identification of 4405 articles containing the keyword terms “biopsy,” “bone tumors,” and “soft tissue tumors.” Clinical articles were excluded on the basis of the abstract content if they represented case reports, review or opinion articles, or technique descriptions or if the subject was not biopsies. The remaining thirty-nine articles that reported data limited to the biopsy of bone and soft-tissue tumors were reviewed by four orthopaedic surgeons (F.T., C.E., D.D., and C.F.) with clinical experience in the diagnosis and treatment of patients with bone and soft-tissue tumors. After review of the full text, eighteen of the thirty-nine articles were excluded because they did not allow determination of the diagnostic accuracy of the biopsies. In addition to this primary search, we performed a secondary search by examining all of the references cited in the included articles retrieved in the primary search; no additional references were found. There was no disagreement among the authors regarding the level of evidence of any of the twenty-one articles that

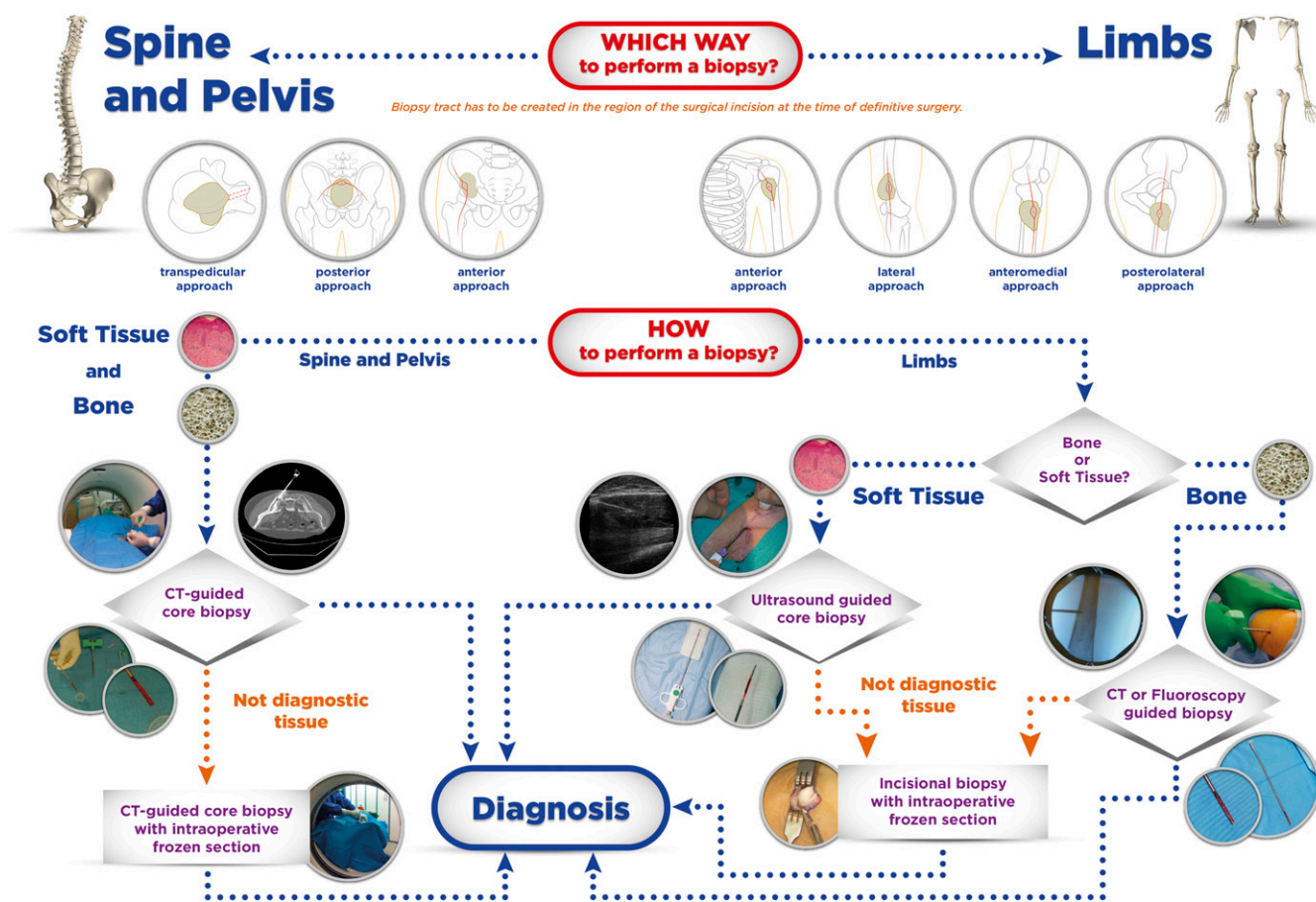


Fig. 1

Flow chart showing the recommended biopsy approaches for various anatomic regions. The biopsy techniques are shown according to the location of the lesion. In the spine and pelvis, a CT-guided core needle biopsy is recommended. If the resulting tissue is nondiagnostic, it is necessary to perform a repeat CT-guided biopsy in conjunction with frozen section analysis. In an extremity, the recommendation for musculoskeletal lesions is still a percutaneous biopsy technique, although it is preferable to use ultrasound guidance for soft-tissue tumors and CT or fluoroscopy guidance for bone tumors. An incisional biopsy with frozen section histology tissue should be performed if the resulting tissue is nondiagnostic.

TABLE I Articles Included in the Present Study\*

Article	No. of Biopsies	Tissue Types	Biopsy Types	Imaging Guidance	Diagnostic Accuracy
Pohlig et al., 2012 <sup>3</sup>	48	Bone	CNB, IB	No	100% CNB, 93.3% IB
Ng et al., 2010 <sup>4</sup>	432	ST	CNB	No	77.2%
Yang and Damron, 2004 <sup>5</sup>	50	ST	FNA, CNB	No	64% FNA, 83% CNB
Kasraeian et al., 2010 <sup>6</sup>	57	ST	FNA, CNB, IB	No	75.4% FNA, 80.7% CNB, 100% IB
Yang et al., 2010 <sup>7</sup>	508	Bone, ST	CNB	Ultrasonography for ST, CT for bone	89%
Adams et al., 2010 <sup>8</sup>	233	Bone, ST	CNB	No	91%
Serpell and Pitcher, 1998 <sup>9</sup>	31	ST	CNB	No	84%
López et al., 2005 <sup>10</sup>	188	ST	CNB	Ultrasonography	92%
Skrzynski et al., 1996 <sup>11</sup>	62	Bone, ST	CNB, IB	No	87% CNB, 96% IB
Liu et al., 2004 <sup>12</sup>	37	ST	CNB	Ultrasonography	89%
Heslin et al., 1997 <sup>13</sup>	164	ST	CNB, IB	No	93% CNB, 94% IB
Sung et al., 2009 <sup>14</sup>	309	Bone, ST	CNB	Ultrasonography for ST, CT or fluoroscopy for bone	90.6%
Rimondi et al., 2008 <sup>15</sup>	430	Bone	CNB	CT	93.3%
Ashford et al., 2006 <sup>16</sup>	271	Bone, ST	CNB, IB	CT	90.9% CNB, 100% IB
Carrino et al., 2007 <sup>17</sup>	45	Bone, ST	FNA, CNB	MRI	64% FNA, 83% CNB
Dupuy et al., 1998 <sup>18</sup>	221	Bone, ST	FNA, CNB	CT	80% FNA, 93% CNB
Hau et al., 2002 <sup>19</sup>	359	Bone, ST	FNA, CNB	CT	63% FNA, 74% CNB
Issakov et al., 2003 <sup>20</sup>	215	Bone, ST	CNB	CT	90%
Mitsuyoshi et al., 2006 <sup>21</sup>	163	Bone, ST	CNB	No	88%
Ogilvie et al., 2006 <sup>22</sup>	120	Bone, ST	FNA, CNB	No	75% FNA, 81% CNB
Torriani et al., 2002 <sup>23</sup>	74	Bone, ST	CNB	Ultrasonography	96%

\*CNB = core needle biopsy, IB = incisional biopsy, ST = soft tissue, and FNA = fine needle aspiration.

were included in the study (Table I)<sup>3-23</sup>. The included articles were then studied to determine the accuracy of each biopsy method for diagnosing bone and soft-tissue tumors. The cost of the biopsy procedure was noted if available, although unfortunately the references did not typically clarify what was included in the reported costs. Finally, guidelines for safe and effective biopsy of musculoskeletal tumors were inferred from the results of the review.

### Source of Funding

No external funding was utilized for this investigation.

### Results

The current literature has not clarified the optimal biopsy technique (fine needle aspiration, core needle biopsy, or incisional biopsy) for the diagnosis of bone and soft-tissue tumors<sup>3-23</sup>. Certain anatomic locations and histologic types were associated with diagnostic difficulty. Vertebral tumors had the lowest diagnostic accuracy<sup>18</sup>. Myxoid, infection, and round cell histologies were associated with the lowest diagnostic accuracy<sup>19</sup>.

Fine needle aspiration (costing \$1060) had a lower diagnostic accuracy compared with core needle biopsy (costing \$1106)<sup>6</sup>. Incisional biopsy was more accurate than percuta-

neous biopsy but more expensive, ranging from \$4321.25 to \$7234.00<sup>6</sup>. However, the accuracy differences did not reach significance. For deep musculoskeletal tumors, incorporation of ultrasonographic or CT (computed tomography) guidance is easy and safe, and it can be useful for increasing the accuracy of percutaneous biopsy<sup>10,15</sup>. Moreover, the advantages of percutaneous compared with incisional techniques are the low risk of tumor contamination of adjacent tissue and its minimally invasive nature<sup>1</sup>.

We propose literature-based guidelines for the biopsy of musculoskeletal tumors (Fig. 1). Regardless of the biopsy technique, general oncologic rules should always be followed. As bone and soft-tissue tumors are usually histologically heterogeneous, multiple samples are commonly required to establish a diagnosis. Although a biopsy procedure will not lead to metastatic dissemination, it can spread tumor cells locally and thus increase the risk of local recurrence. It should be assumed that the biopsy track may be contaminated and needs to be resected during the definitive tumor surgery. It is mandatory that the biopsy be performed at the planned surgical incision site so that that tissue will be included in the surgical

specimen. The biopsy track must not violate more than one anatomic compartment and must be away from any neurovascular bundle<sup>24</sup>.

For a bone biopsy, the shortest route to the lesion is not necessarily the optimal one. In general, the biopsy should be planned carefully with the use of MRI (magnetic resonance imaging) on the basis of the site of the definitive surgery. An improperly performed biopsy can complicate patient care and can sometimes eliminate treatment options.

For a soft-tissue biopsy, the site should be located directly over the tumor, at the point where the lesion is closest to the surface as shown by MRI, and the raising of flaps or violation of tissue planes superficial to the tumor should be avoided.

### Discussion

**B**iopsy is a key step in the diagnosis of bone and soft-tissue tumors. However, we found that the current literature has not clarified the optimal biopsy technique for the diagnosis of such tumors<sup>3-23</sup>. Core needle biopsy appeared to be more accurate than fine needle aspiration, and incisional biopsy appeared to be more accurate than either of these percutaneous methods, but the differences in diagnostic accuracy did not reach significance.

Technical considerations include proper location and orientation of the biopsy incision as well as meticulous hemostasis. It is necessary to obtain tissue for a histologic diagnosis without spreading the tumor and compromising the treatment<sup>24</sup>. The surgeon should not open any compartmental barrier, anatomic plane, joint space, or tissue area around a neurovascular bundle and should avoid creating a hematoma. The biopsy should be planned carefully on the basis of the location of the intended definitive surgery, and it should be performed by an expert orthopaedic surgeon. Improperly done, it can complicate patient care and sometimes even eliminate treatment options<sup>1</sup>.

### Bone Biopsies

Incisional biopsy has long been considered the gold standard for bone tumors. It is reasonable to assume that the risk of local contamination is higher than that for the percutaneous techniques and is related to the width of the biopsy track and the adequacy of hemostasis. As a rule, any extraosseous extension of a malignant bone tumor is as representative of the tumor as the osseous component is, and it would therefore be the preferred biopsy site. Violating the cortex of a bone predisposes the patient to a pathologic fracture and is recommended only if there is no extraosseous extension of the tumor<sup>24</sup>. When a purely intraosseous bone lesion is biopsied, it is necessary to create a cortical window of an appropriate shape. Clark et al.<sup>25</sup> reported that use of an oblong window with rounded ends resulted in the greatest strength of the residual bone; in contrast, rectangular holes with square or rounded corners act as stress risers and may lead to fracture. Furthermore, increasing the width of the window caused a significant reduction in strength but increasing the length did not. In challenging situations (e.g., Ewing sarcoma located in the spine or pelvis), bleeding can necessitate a transfusion.

Incisional biopsy is usually indicated when the diagnosis following a percutaneous biopsy is inconclusive or does not correspond to the clinical presentation and radiographic findings<sup>12,24</sup>. Recent studies increasingly indicate similar diagnostic accuracy for percutaneous compared with incisional biopsy<sup>3,8,14</sup>. In addition, percutaneous biopsy has a lower risk of complications (0 to 10%) compared with incisional biopsy (up to 16%)<sup>2</sup>. The main complications are bleeding, neuroapraxia, and infection<sup>26</sup>. During percutaneous biopsy, the use of CT or fluoroscopic guidance provides excellent spatial localization of the lesion<sup>1</sup>. Other advantages are the low risk of contamination and the minimally invasive nature<sup>27</sup>. This type of biopsy can be performed in an outpatient clinic with use of local anesthesia, so the cost and time are less than those for incisional biopsy<sup>6,11</sup>.

Pohlig et al.<sup>3</sup> retrospectively compared core needle biopsy with incisional biopsy in forty-eight bone tumors. The diagnostic accuracy was 100% for core needle biopsy and 93.3% for incisional biopsy; this difference was not significant ( $p > 0.05$ ). Other recent studies also indicated no difference in accuracy between core needle and incisional biopsy<sup>8,14</sup>.

For deep lesions (e.g., in the pelvis or spine), percutaneous biopsy is challenging and has a diagnostic accuracy less than that of incisional biopsy. In these cases, CT guidance can be useful for increasing the accuracy of percutaneous biopsy and reducing complications and has now become the procedure of choice<sup>15</sup>.

### Soft-Tissue Biopsies

Incisional biopsy has long been the gold standard for soft-tissue tumors, yielding a diagnostic accuracy of 94% to 100%. However, it is expensive and has a complication rate of up to 16%, including hematoma, tumor spread, and wound problems that may interfere with future treatments<sup>1,2,28</sup>. As a result, less invasive alternatives have been developed<sup>4,6</sup>.

Fine needle aspiration is usually accepted for documentation of metastases and local recurrences, especially if prior samples are available for comparison<sup>4</sup>. Although this technique distinguishes mesenchymal from metastatic tumors, malignant from benign lesions, and high from low-grade sarcomas, it is unable to precisely subtype sarcomas<sup>4</sup>. A wide range of sensitivities (86% to 100%), specificities (36% to 100%), and diagnostic accuracies (21.9% to 98%) have been reported in the literature. However, those studies usually excluded nondiagnostic samples, reducing the reliability of the published values<sup>6</sup>. Ng et al.<sup>4</sup> retrospectively examined the diagnostic accuracy of 432 fine needle aspirations of soft-tissue masses in the extremities. They reported that the nature of the lesion was indeterminate or the sample was inadequate in 8.1% of the cases. The accuracy was 77.2% for subtyping and 95.2% for grading of malignant lesions. One-quarter of all patients required a second biopsy before definitive treatment.

Core needle biopsy has evolved as an alternative to fine needle aspiration. This technique improves the determination of the histologic subtype and grade compared with fine needle aspiration<sup>6</sup>. Sensitivities of 81.8% to 100%, specificities of 91% to 100%, and diagnostic accuracies of 72.7% to 100% have

been reported. The reported complication rates are only 0.1% to 1.1%. However, as in the case of fine needle aspiration, the studies often excluded nondiagnostic samples, thus falsely elevating the accuracy rate<sup>6</sup>.

Although much literature exists regarding the diagnostic yield of the individual biopsy techniques, we identified only two studies that compared the accuracy of multiple biopsy techniques in the same soft-tissue tumor<sup>5,6</sup>. Yang and Damron<sup>5</sup> compared fine needle aspiration and core needle biopsy for the diagnosis of the same soft-tissue mass and found core needle biopsy to be 83% accurate and fine needle aspiration to be 64% accurate. Kasraeian et al.<sup>6</sup> prospectively studied fifty-seven patients with soft-tissue masses, performing fine needle aspiration followed by core needle biopsy followed by incisional biopsy of the same mass. Incisional biopsy was 100% accurate even for determining the exact diagnosis. The accuracy of the general diagnosis was 75.4% for fine needle aspiration and 80.7% for core needle biopsy. However, the accuracy of the exact diagnosis was only 33.3% for fine needle aspiration and 45.6% for core needle biopsy. Therefore, Kasraeian et al. recommended incisional biopsy for the diagnosis of soft-tissue masses.

Ultrasonographic guidance of percutaneous soft-tissue biopsies has been reported to result in high accuracy<sup>26</sup>. Real-time multiplanar visualization of the needle not only results in a safe procedure by visualizing vital structures but also permits selective sampling of areas within the tumor, avoiding cystic or necrotic areas. The biopsy needle is inserted in the same longitudinal plane as the ultrasonographic guidance to aid visualization of the needle<sup>26</sup>.

In summary, incisional biopsy appears to be the most accurate modality but the evidence is not strong enough to recommend one biopsy technique over another<sup>29</sup>. This lack of evidence should encourage investigators to analyze the diagnostic accuracy of these various biopsy techniques.

### Recommendations

A bone or soft-tissue tumor biopsy is a simple technical procedure but may be conceptually difficult<sup>29</sup>. The goal of biopsy is to obtain diagnostic tissue while minimizing morbidity, limiting potential tumor spread, and avoiding interference with future surgical treatment<sup>6</sup>. Because of the low risk of contamination and low cost, core needle biopsy appears to be more suitable than incisional biopsy for the diagnosis of bone and soft-tissue tumors<sup>30</sup>. Furthermore, the use of imaging guidance increases the diagnostic accuracy of such musculoskeletal biopsies

and reduces the risk of complications<sup>20</sup>. However, if a percutaneous biopsy is nondiagnostic, a subsequent incisional biopsy should be performed<sup>1</sup>.

The biopsy guidelines presented in this article are based on our review of the current literature and are outlined according to anatomic region in Figure 1. In the spine and pelvis, we recommend a CT-guided core needle biopsy for both bone and soft-tissue tumors. If the tissue obtained is nondiagnostic, we recommend a repeat CT-guided biopsy with histologic analysis of frozen sections. Our recommendation for musculoskeletal lesions in the extremities is still a percutaneous biopsy, although we recommend the use of ultrasonographic guidance for biopsies of soft-tissue tumors and CT or fluoroscopy guidance for biopsies for bone tumors. Again, if the tissue obtained with the percutaneous biopsy is nondiagnostic, an incisional biopsy with analysis of frozen sections should be performed.

The lack of evidence in the current literature regarding the superior accuracy of any particular biopsy technique for the diagnosis of bone and soft-tissue tumors justifies a minimally invasive technique as a first choice. This lack also suggests the need for a prospective randomized study analyzing the diagnostic accuracy, morbidity, and cost of percutaneous or incisional biopsy for the diagnosis of bone and soft-tissue tumors. ■

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