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Initial Diagnostic Management of Pediatric Bone Tumors

Rodrigo B. Interiano[a,b], **Alpin D. Malkan**[a], **Amos H.P. Loh**[a,c], **Nathan Hinkle**[a,b], **Fazal N. Wahid**[a], **Armita Bahrami**[d], **Shenghua Mao**[e], **Jianrong Wu**[e], **Michael W. Bishop**[f,g], **Michael D. Neel**[a], **Robert E. Gold**[h], **Bhaskar N. Rao**[a], **Andrew M. Davidoff**[a,b], and **Israel Fernandez-Pineda**[a,b,*]

[a] Department of Surgery, St. Jude Children's Research Hospital, Memphis, TN

[b] Department of Surgery, University of Tennessee Health Science Center, Memphis, TN

[c] Department of Paediatric Surgery, KK Women's and Children's Hospital, Singapore

[d] Department of Pathology, St. Jude Children's Research Hospital, Memphis, TN

[e] Department of Biostatistics, St. Jude Children's Research Hospital, Memphis, TN

[f] Department of Oncology, St. Jude Children's Research Hospital, Memphis, TN

[g] Department of Pediatrics, University of Tennessee Health Science Center, Memphis, TN

[h] Department of Radiological Sciences, St. Jude Children's Research Hospital, Memphis, TN

Abstract

Background—Osteosarcoma (OS) and the Ewing sarcoma family of tumors (ESFT) are the most common primary pediatric bone malignancies. We sought to assess the diagnostic accuracy of initial tumor biopsies in patients with OS or ESFT at a pediatric cancer center.

Methods—All biopsies performed at initial presentation of patients with OS or ESFT at our institution from 2003 to 2012 were retrospectively reviewed. Diagnostic accuracy and incidence of complications were correlated with study variables using logistic regression analysis.

Results—One hundred forty-two biopsies were performed in 105 patients (median age 13.4 years, range: 1.8-23.0), 104 (73.2%) OS and 38 (27.8%) ESFT. Thirty-one (21.8%) were performed on metastatic sites. Eighty-five (76.6%) of 111 primary site biopsies were open procedures, and 26 were percutaneous (23.4%). Primary site biopsies were successful in 94.1% of open and 73.1% of percutaneous procedures. Odds of obtaining a successful diagnostic specimen were 7.8 times higher with open approach (CI: 1.6-36.8). Metastatic site biopsies were successful in 66.7% of percutaneous and 100% of open and thoracoscopic procedures.

[*]**Corresponding Author:** Israel Fernandez-Pineda, MD, Department of Surgery, St. Jude Children's Research Hospital, 262 Danny Thomas Place, Memphis, TN 38105, israel.fernandez-pineda@stjude.org, Telephone: (901) 595-4060, Fax: (901) 595-6621.

Conclusion—Biopsy of metastatic sites was equal to primary site in obtaining diagnostic material with the added benefit of accurate staging, with few adverse events and high diagnostic yield.

Keywords

Biopsy; Tumor; Osteosarcoma; Ewing sarcoma; Pediatrics; Diagnosis

Osteosarcoma (OS) and Ewing sarcoma family of tumors (ESFT) are the two most common primary pediatric bone malignancies, accounting for 56% and 34% of bone cancer in children, respectively [1]. While studies incorporating the use of neoadjuvant and adjuvant chemotherapy in standardized treatment regimens have improved the outcomes for patients with localized bone malignancies, 5- and 10-year survivals for these patients continue to be below 75% [2-5]. Metastatic disease fares worse for both histologies, with 5-year survival rates of less than 30%. An even worse survival has been seen in patients who present with extra-pulmonary metastatic disease at initial diagnosis [6-8]. Rapid diagnosis and accurate staging are critical to stratifying patients into appropriate therapeutic regimens.

Procurement of adequate diagnostic pathologic specimens is key to determining the correct diagnosis, whether collected from the primary lesion or a suspected metastatic site. As recently noted by several collaborative groups, the most important prognostic factor for OS and ESFT is presence of metastases, with the lungs being the most common metastatic site in both histologies [2, 7, 9]. Biopsy of suspected metastatic lung nodules may be performed by an open, minimally-invasive (e.g. thoracoscopy), or percutaneous approach [10-11]. Staging these patients with tissue samples and appropriate imaging will help delineate the appropriate treatment plan depending on the spread of these tumors [12-13]. OS is somewhat unique in that resection of metastatic sites has been shown to provide an improvement in survival; therefore, biopsies of suspected metastatic sites must be considered for accurate staging [3, 7, 14-17].

Recently, we performed a large, retrospective review of all tumor biopsies performed at our institution over a ten-year period [18]. In this review, we noted a high success rate of obtaining a successful pathologic specimen. A subgroup analysis was then performed to assess the initial diagnostic management of bone tumors in children and adolescents. We sought to assess the diagnostic accuracy and describe the initial approach to tumor biopsies in patients diagnosed with OS or ESFT.

1. Patients and methods

1.1. Patient and procedures

Following Institutional Review Board approval, we retrospectively reviewed the records of all patients diagnosed with either OS or ESFT who underwent their initial tissue biopsies at St. Jude Children's Research Hospital between January 1, 2003 and December 31, 2012. We collected data regarding patient characteristics including age at time of procedure, weight, height, race, gender, primary diagnosis, histologic result of biopsy and pre-procedure laboratory values; and procedure-related characteristics including type of anesthesia used,

biopsy site, mode of biopsy and imaging modality if any was used. Percutaneous biopsies were performed by both surgeons and interventional radiologists with imaging modalities being used to acquire the biopsy. We also collected data on whether the biopsy site was a primary versus a distant lesion. Overweight was defined as a body mass index (BMI) ≥ 85th percentile for children of the same age and sex, while obesity was defined as a BMI ≥ 95th percentile.

All adverse events occurring within the 30-day post-procedure period were reviewed and graded 1–4 according to Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 [19]. No patients in this sub-group analysis died within this 30-day post-procedure time period. The diagnostic accuracy of a biopsy has been previously described [20]. Briefly, we assessed the conclusiveness of the pathologist's report, compared congruency of the histologic result obtained at subsequent biopsies, and the patient's clinical course. We considered a biopsy to be “successful” if it was deemed “diagnostic” and the biopsy had acquired an adequate volume of lesional material yielding a definitive histologic diagnosis. The biopsy was deemed “unsuccessful” if was it was deemed “insufficient for diagnosis” or “non-diagnostic” where lesional material was either obtained or not obtained, respectively.

1.2. Statistical analysis

Correlation of study variables with diagnostic accuracy and incidence of complications were analyzed using univariate logistic regression. Using stepwise selection, all factors entered into multivariable logistic regression models at level of $P<0.2$. The relationship of selected laboratory test values and the occurrences of post-procedural blood transfusions and infections were analyzed using Pearson Correlation and univariate logistic regression.

2. Results

2.1. Patient and procedure characteristics

One hundred forty-two biopsies were performed in 105 patients with a median age at biopsy of 13.4 years (range: 1.8-23.0). Patient characteristics are summarized in Table 1. Fifty-eight (55.2%) patients were females, and the majority (65.7%) of patients were Caucasian (69 white, 34 black, 2 other). Median BMI of these patients was 19.8 (range: 13.3-42.1); however, by BMI percentile adjusted for age and sex, 10 (9.5%) patients were overweight and 22 (21.0%) patients were obese. One hundred four (73.2%) biopsies proved to be OS and 38 (27.8%) proved to be ESFT by final pathology (Table 2).

One hundred eleven (78.2%) procedures were performed on the primary lesion. Procedure characteristics are summarized in Table 2. Of these biopsies, 85 (76.6%) were performed via an open approach, with the remaining 26 (23.4%) procedures done percutaneously. Primary lesions yielded a diagnostic specimen in 80 (94.1%) open procedures and 19 (73.1%) percutaneous biopsies. Distant sites were targeted for biopsy in 31 (21.8%) procedures, while 15 (14.3%) patients were found to have metastatic disease by pathology. Twenty-five (80.6%) biopsies were performed on the lung and 3 (9.7%) were performed on bony skip lesions. The remaining suspected metastatic sites were the following: a liver lesion in a

patient with ESFT, a chest wall lesion in a patient with OS from a large, pre-celiac intra-abdominal tumor, and a sacral mass in a patient with a primary distal femoral OS. The approaches for the metastatic sites were open, thoracoscopic, or percutaneous in 10 (32.3%), 15 (48.4%), and 6 (19.3%) procedures, respectively, with success rates of 100%, 100%, and 66.7%. The odds of obtaining a successful diagnostic specimen were 7.8 times higher when using an open approach at all sites (CI: 1.6-36.8) (Table 2).

Twenty-three (21.9%) patients had biopsies performed of both the primary lesion and a distant site; however only 10 (43.5%) of these patients had procedures performed the same day. Pulmonary lesions in 19 (82.6%) procedures were the most common distant sites approached when both lesions were being biopsied. Thirteen (68.4%) of these biopsies were approached thoracoscopically, whereas the others were open in 5 (26.3%) and percutaneous in 1 (5.3%). The percutaneous biopsy in this group was the only procedure which yielded a non-diagnostic pathologic specimen. Six (5.7%) patients had eight biopsies performed on only a distant site biopsied with presumed malignancy of the primary lesion. Eleven (10.5%) patients were confirmed to have metastatic osteosarcoma at initial diagnosis, while only 2 (1.9%) ESFT patients presented with metastatic disease. Only one of these patients had an unsuccessful biopsy performed (percutaneous lung biopsy) which was repeated via an open approach 6 days later.

2.2. Repeat and unsuccessful biopsies

Thirteen (12.4%) patients had repeat biopsies of a previously sampled site; all but one were due to an unsuccessful initial biopsy. In all cases, the same location was re-biopsied. One patient required a total of three biopsies from the primary lesion after two unsuccessful procedures yielded non-diagnostic pathologic specimens.

2.3. Adverse Events

Four (2.8%) adverse events were seen after 142 procedures. One patient required transfusion of packed red blood cells after a percutaneous needle biopsy of a femoral lesion which proved to an osteosarcoma. The patient had a pre-operative hematocrit of 25% and International Normalized Ratio of 1.24; however, hematocrit trended down to 21% post-procedurally. A second patient had a post-operative hematoma after an open biopsy of a femoral lesion, but did not require transfusion. This same patient later developed a pathological fracture on post-procedure day nine, although it is unclear if this was the site of the biopsy. Two patients developed wound infections after open biopsies, requiring treatment with antibiotics. One of the two developed dehiscence of the wound and required additional local wound care and debridement in the operating room. Both patients had normal absolute neutrophil counts pre-operatively. None of these patients required amputation secondary to the complications, and none were noted to have local recurrences due to the local complications. By univariate and multi-variable regression analysis, there were no predictors of adverse events seen for these procedures.

3. Discussion

In our series, biopsy of the primary tumor or metastatic sites for the initial diagnosis of bony tumors, specifically OS and ESFT, in children is associated with a high (>90%) diagnostic yield at the initial approach. A second attempt after an unsuccessful biopsy approached a success rate of 100%. Biopsies can be targeted to the primary or suspected metastatic site; however, a diagnostic yield from a metastatic site will further assist in appropriate staging of the patient's malignancy. As others have previously shown, 11-18% of patients present with metastatic OS at initial presentation, while our review showed similar results [7, 8, 21]. Although a high percentage of our patients who had metastatic sites biopsied also had biopsies performed of the primary lesions, it may be beneficial to attempt to target the metastatic site alone so as to not cause any potential adverse effects at the primary lesion such as iatrogenic pathologic fracture, infection at the site, and potential seeding of tumor cells in the area. Diagnosis via metastatic sampling eliminates the need to later resect a biopsy tract at the primary site as part of definitive local control measures. The importance of establishing the diagnosis of metastases in both OS and ESFT has been extensively reported; while localized tumors have been associated with survival rates of 65-70% for OS [3-5], and up to 83% for ESFT [22], the presence of metastatic lesions in both histologies has historically resulted in survival rates of 32% or less [7, 8, 23]. With the advent of advanced technologies such as higher resolution CT imaging, navigational bronchoscopy, wire localization, lung tattooing and minimally-invasive approach to procedures in the chest, lung nodules are becoming increasingly easier to access while minimizing potential adverse events on the patient [24-29].

Biopsies performed for bony malignancies in the pediatric population were associated with a low rate of adverse events in our cohort, even lower than has been shown previously when taking multiple tumor histologies into account. Although these procedures can be associated with life-threatening events [18], we did not observe any in this study. Mankin and colleagues reported in 1996 a large study of patients who underwent biopsy for bone or soft-tissue sarcomas and noted an adverse event rate of >10%, although this study population was different in that the mean age (and standard deviation) was 38 ± 21.8 years and included a wide range of different bony and soft tissue histologic diagnoses. Some have described immediate post-operative events such as fractures, hematomas, and infection, while others have reported tumor seeding leading to local progression, as well as poor technical biopsies requiring larger resections of the previous biopsy site [30-32]. We identified a few instances of bleeding and infection and also observed one patient with a post-procedural pathological fracture, although the location of the fracture in relation to the biopsy is unclear. Our study focused on the immediate post-operative 30-day adverse events, and thus did not assess for long-term complications from the biopsy. However, local recurrence as well as needle tract recurrences can further worsen a patient's prognosis [33-34].

The technical approach to the biopsy is also of utmost importance [35]. As might be expected, a biopsy performed through an open approach was more likely to yield a successful diagnostic specimen as compared to both thoracoscopic and percutaneous approaches. However, there were no unsuccessful thoracoscopic biopsies observed in our study. In fact, there were only two unsuccessful biopsies on the 31 suspected metastatic

sites, both of which were performed percutaneously. There are, however, special instances where percutaneous biopsies appear to be more beneficial, while also noting that the success rate for percutaneous biopsies was greater than 70%. For instance, lesions of the tibia which are proximal and medial where there is little soft tissue coverage may be more amenable to a percutaneous approach. During local control, the biopsy tract and overlying skin will need resection; this can result in significant loss of soft tissue in this area [36]. Frequently in younger, thinner patients, a larger skin graft will be required to cover the gastrocnemius flap often used for coverage and extensor mechanism reconstruction. An open biopsy in this area also carries a higher risk of post-operative hematoma, which in this area of thin soft tissue, may migrate remotely down the extremity. Tumors in deep locations (e.g. pelvis) may also be more easily approached via a percutaneous approach. A percutaneous approach greatly diminishes the amount of tissue that needs to be resected and minimizes hematomas. In our series, only one adverse event was seen in a percutaneous biopsy, with adjunct imaging providing further assistance in obtaining tissue. Additionally when metastatic lesions are suspected, biopsy of these can give the definitive tissue diagnosis, answer the question of whether there is metastatic disease and avoid biopsy in this high risk area altogether. The performing or supervising physician should also be intimately aware of the approach of limb-salvage procedures for these patients as previous incisions will need to be resected during the definitive resection [36], and improperly performed biopsies may make definitive resections difficult to perform. For open biopsies, a small longitudinal incision which allows access to adequate tissue should be made. Transverse incisions are contra-indicated as they will require wider resection at the time of the definitive procedure, as well as planning for muscle flaps and closure of the wound. Furthermore, maintaining hemostasis is critical, as large hematomas can dissect through tissue planes, contaminate entire extremities, and make limb-sparing surgical procedures impossible [35].

The incidence of obese patients (21.0%) in our cohort is high, although it does not differ from recent population-based studies assessing prevalence of obesity in childhood [37]. Recently, Novais and colleagues demonstrated obesity to be a major risk factor for developing complications after osteotomy [38], while others have similarly focused on other orthopedic procedures [39-41]. Moore et al. also reported obesity to be an independent risk factor for major wound complications after soft tissue sarcoma resection [42]. While we did not find any association between obesity and adverse events or diagnostic accuracy, some have reported high BMI at diagnosis to be associated with poorer survival in patients with osteosarcoma [43], although Bielack and Kevric noted this finding could be explained by other socioeconomic or healthcare factors [44]. Identifying these patients at potential risk early on may help in the patient education process.

We believe this study will help guide others who are presented with a new patient and a suspected bone neoplasm and determining whether to approach the primary lesion or to consider approaching a suspected metastatic site. This decision should be made on an individualized basis, based on the level of clinical and radiographic suspicion of malignancy. In addition to magnetic resonance imaging and plain radiographs of the primary site, diagnostic evaluations for OS and ESFT include computed tomography of the chest, radionuclide bone scan, and 18-fluorodeoxyglucose positron emission tomography. Diagnostic biopsy approaches focusing on sampling distant lesions and preserving the

primary site may inadvertently create a risk for a number of patients with benign osseous lesions to undergo additional imaging work-up and radiation exposure. Frozen sections of metastatic lesions can also provide information in making the appropriate diagnosis without having to approach the primary lesion. A multidisciplinary review of primary bone lesions by surgeons, radiologists and oncologists will optimize the identification of best candidates for further metastatic workup and biopsy. Lesions that are indeterminate by clinical history or imaging appearance should still undergo primary site biopsy.

In conclusion, performing a biopsy for a suspected bone neoplasm should mandate a multidisciplinary approach to ensure a timely diagnosis and treatment plan. Although diagnostic inaccuracy and adverse events can hinder this process, consideration must be given to the different options for approach as well as lesions in each individual patient as complications can lead to delay in diagnosis, delay in treatment, and the risk of hindering more conservative surgical resections. Biopsy of metastatic sites was equal or superior to primary sites in obtaining diagnostic material, with the potential added benefit of assisting in staging, while not unexpectedly, we observed open biopsies to have an improved diagnostic accuracy. Lastly, in this study we provide some general guidelines on how to approach a bone tumor at both the primary and metastatic sites. We believe this study will serve to highlight some important considerations for these complex cases.

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Table 1

Univariate analysis of patient characteristics associated with occurrence of inadequate or non-diagnostic biopsy result and post-operative complications.

Characteristic	No. of initial procedures	Inadequate / non-diagnostic result		Post-procedural adverse events	
Patient Characteristics					
All patients	142	14 (9.9)		4 (2.8)	
Categorical variables	**n (%)**	**n (%)**	***P***	**n (%)**	***P***
Gender			0.9491		0.2336
Male	62 (43.7)	6 (42.9)		3 (75.0)	
Female	80 (56.3)	8 (57.1)		1 (25.0)	
Ethnicity			0.1580		0.7717
White	97 (68.3)	12 (85.7)		3 (75.0)	
African-American	43 (30.3)	2 (14.3)		1 (25.0)	
Others	2 (1.4)	0 (0)		0 (0)	
Obese**			0.0967		0.1017
Yes	27 (19.0)	4 (28.6)		3 (75.0)	
No	115 (81.0)	10 (71.4)		1 (25.0)	
Continuous variables	**Median (range)**	**Median (range)**	***P***	**Median (range)**	***P***
BMI	19.7 (13.3-42.1)	22.7 (17.5-28.4)	0.7966	27.0 (18.9-29.1)	0.2082
Weight (kg)	53.6 (11.8-115.1)	58.2 (39.6-94.1)		71.0 (59.7-90.8)	
Height (cm)	159.0 (83.7-188.0)	165.0 (129.6-182.6)		171.3 (158.0-177.8)	
Age at biopsy (years)	13.4 (1.8-23.0)	15.1 (8.3-20.0)	0.2656	14.0 (11.8-20.0)	0.3604

** Body mass index of >30 if age greater than or equal to 20 or BMI percentile greater than 95% if age less than 20.

Table 2

Univariate analysis of procedure and disease characteristics associated with occurrence of inadequate or non-diagnostic biopsy result and post-operative complications.

Characteristic	No. of initial procedures	Inadequate / non-diagnostic result		Post-procedural adverse events	
Patient Characteristics					
All patients	142	14 (9.9)		4 (2.8)	
Categorical variables	**n (%)**	**n (%)**	***P***	**n (%)**	***P***
Anesthesia			**0.0439**		0.9798
General	137 (96.5)	13 (92.9)		4 (100)	
Local/Regional	5 (3.5)	1 (7.1)		0 (0)	
Biopsy Site			0.9328		0.9990
Primary lesion	111 (78.2)	12 (85.7)		4 (100)	
Metastatic site	31 (21.8)	2 (14.3)		0 (0)	
Mode of biopsy – primary lesion			**0.0055**		0.9990
Open	85 (76.6)	5 (41.7)		3 (75.0)	
Percutaneous	26 (24.3)	7 (58.3)		1 (25.0)	
Mode of biopsy – metastasis					
Open	10 (32.3)	0 (0)		0 (0)	
Minimally-invasive	15 (48.4)	0 (0)		0 (0)	
Percutaneous	6 (19.3)	2 (100)		0 (0)	
Use of radiographic image guidance			0.4767		0.8765
Yes	111 (78.2)	12 (85.7)		3 (75.0)	
No	31 (21.8)	2 (14.3)		1 (25.0)	
Repeat biopsy at a previous site			0.7211		0.9660
Yes	14 (9.9)	1 (7.1)		0 (0)	
No	128 (90.1)	13 (92.9)		4 (100)	
Disease characteristics					
Categorical variables	**n (%)**	**n (%)**	***P***	**n (%)**	***P***
Final pathology			0.0642		0.8865
Osteosarcoma	104 (73.2)	7 (50.0)		3 (75.0)	
Ewing sarcoma family of tumors	38 (27.8)	7 (50.0)		1 (75.0)	

* Bold values are significant at $P<0.05$