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What Is the Clinical Impact of Sending Tissue for Histopathology During Surgery for Known, Diffuse Metastatic Disease to Bone?

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Abstract. *Background/Aim: During surgery for patients with known, diffuse metastatic bone disease (MBD), lesional tissue is routinely sent for pathological evaluation. However, there are limited data to assess whether there is a role for histopathology for MBD despite time and cost of interpretation, as well as whether a positive sample changes the subsequent treatment course. Patients and Methods: Sixty-six cases from 2017 to 2020 were reviewed retrospectively. The median age at surgery was 63.5 years (range of 23 to 84 years), and the primary tumor was most frequently breast (24.2%, n=16), renal (21.2%, n=14) or lung (15.2%, n=10). The most common location of MBD was the femur (60.6%, n=40). Results: The overall yield of a positive tissue sample of MBD was 77.3% (n=51). The positive rate from sending intramedullary reamings was 65.4% (n=17 of 26). Among the 66 cases (63 patients), a change in the subsequent clinical management was recorded in 9.1% (n=6). The most common change was related to the medication regimen (n=5), with one change related to recognition of the carcinoma origin via histology, which was previously unknown. Conclusion: Despite the routine practice of sending tissue for histology during surgery for known and diffuse MBD, a change in the subsequent clinical management is uncommon. Prior to sending tissue, surgeons should discuss this practice with the multidisciplinary care team on a per-patient basis.*

Metastatic bone disease (MBD) is a frequently encountered entity with a high estimated prevalence. Furthermore, costs-of-care for patients with MBD are rapidly increasing (1). Various tumors metastasize to the bone, though most originate from the breast, kidneys, prostate, lungs, or thyroid (2). MBD has a predilection for extremity long bones and the current standard of care advocates for surgical intervention in cases of impending or actual pathological fracture (3-5).

When MBD is suspected, tissue confirmation is critical to rule out a primary sarcoma which would require a different treatment. Namely, patients with no history of cancer or with a recent or active history of cancer without metastasis deserve biopsy for unconfirmed skeletal lesions. Therefore, when a new diagnosis of skeletal metastasis is made clinically or radiographically, an intraoperative biopsy should be performed to rule out a primary tumor before definitive treatment (6, 7).

However, for surgery in the setting of known and widespread MBD, lesional tissue is still sent for interpretation by histopathology. For example, intramedullary reamings may be sent during internal fixation of long bone MBD (8-12). Additionally, as is done in our institution, lesional bone and soft tissue are sent for interpretation, following tumor resection for MBD. Despite the routine practice of sending tissue in this setting, however, there are no identifiable studies in which the subsequent clinical impact is measured. Furthermore, there are costs and time associated with interpreting the tissue, and in certain instances, the tissue volume or quality is insufficient to identify any malignancy at all (13). As such, the purpose of this study was to identify the rate of a positive tissue sample in cases of known, diffuse MBD, and describe any clinical changes thereafter.

Patients and Methods

Following approval from the Institutional Review Board, a prospectively maintained surgical database was queried between 2017 and 2020. One-hundred eighteen patients with MBD were screened. Inclusion criteria were diffuse and multicentric MBD diagnosed prior to definitive treatment, cases with tissue sent during surgical intervention, and patients who received multidisciplinary oncologic care within our tertiary academic medical center. Patients with less than one month follow-up were excluded, as were those with MBD diagnosed on frozen section with no additional tissue sent. The records of 63 patients (66 cases) were then reviewed retrospectively.

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Basic patient and tumor variables were gathered. These included age, primary tumor origin, location of metastasis and/or fracture, and type of surgical intervention. Each case underwent a surgical procedure by the senior author (A.B.), and included internal fixation, resection/intralesional procedure with arthroplasty, resection/intralesional procedure with reconstruction, or resection/intralesional procedure with methylcrylation. Histopathological variables included the largest aggregate tissue volume (cm^3) received, tissue quality description, and final diagnosis, if any. Oncology notes were then reviewed for subsequent changes in management after surgery. Clinical outcomes included additional testing or referrals, changes in medication regimens or interval follow-up, and/or additional procedures as a direct result of the tissue sample. Simply continuing on the same therapy regimen as before surgery was not considered a clinical change as a result of histopathology.

Continuous variables were analyzed using Student's *t*-test, and categorical variables were compared with Fisher's exact test and odds ratios. The overall yield from sending tissue was calculated as the rate of positive diagnoses to total specimens sent, and each of the clinical outcomes were described qualitatively. A *p*-Value of <0.05 was considered statistically significant.

Results

The median age at surgery was 63.5 years (range of 23 to 84 years) and the majority of patients were female (57.6%, n=38) (Table I). Among the 66 cases, the primary tumor was most frequently breast (24.2%, n=16), renal (21.2%, n=14) or lung (15.2%, n=10), and the most common location of MBD was in the femur (60.6%, n=40). For surgery, 39.4% (n=26) underwent internal fixation, 24.2% (n=17) had resection with primary joint arthroplasty, 21.2% (n=14) had resection with modular endoprosthetic reconstruction, and 7.6% (n=5) had a modified Harrington technique with methylcrylation. The remaining 7.6% (n=5) had resection of solitary metastatic sites.

The overall yield of a confirmatory MBD tissue sample was 77.3% (n=51). The positive rate from reamings only cases was 65.4% (n=17 of 26), and the positive rate from resection with primary joint arthroplasty only cases was 76.5% (n=13 of 17). The positive rate in tissue sent during resection with modular endoprosthetic reconstruction was 100% (n=14). Among all cases, the overall mean (standard deviation) volume of tissue received by histology was 166 cm^3 (359.6 cm^3), and there was a trend towards a positive result with a greater volume of tissue [OR=1.009; 95% confidence interval (CI)=0.99-1.019; $p=0.074$). Of the total 66 specimens sent for histopathology review, 13.6% (n=9) had crushing or necrosis and were inadequate for interpretation. There were no instances of a positive sample other than MBD.

Among the total 66 cases (63 patients), a change in clinical management was recorded in 9.1% (n=6) (Table II). The most common change was with medication (n=5). The remaining was a case that was initially diagnosed as metastatic carcinoma of unknown primary and additional surgical tissue revealed a possible sinus or nasal origin prompting additional work-up. Though of note, the further work-up was eventually negative. Lastly, there were no instances of a change in clinical management as a result of a negative tissue sample.

Table I. *Demographics of the patients included (n=63) along with tumor and treatment characteristics of the lesional sites (n=66).*

Variable	n (%)
Age (years)[a]	63.5 (23-84)
Female	38 (57.6)
Male	28 (42.4)
Primary tumor	
Breast	16 (24.2)
Renal	14 (21.2)
Lung	10 (15.2)
Prostate	6 (9.1)
Thyroid	2 (3.0)
Lymphoma	2 (3.0)
Myeloma	3 (4.5)
Other	13 (9.7)
Location	
Femur	40 (60.6)
Acetabulum	10 (15.2)
Humerus	9 (13.6)
Tibia	2 (3.0)
Other	5 (7.6)
Pathological fracture	40 (60.6)
Surgery performed	
Internal fixation	26 (39.4)
Total hip arthroplasty	16 (24.2)
Endoprosthetic reconstruction	14 (21.2)
Modified Harrington	5 (7.6)
Other	5 (7.6)
Metastasis confirmed	51 (77.3)
Tissue received (cm^3)[b]	166 (359.6)
Crushing or necrosis on sample	9 (13.6)

[a]median (range); [b]mean (standard deviation).

Discussion

Despite a high annual volume of patients who undergo surgery for MBD, there are no current data that assess whether sending tissue in the setting of diffuse metastasis affects the subsequent clinical course. The current study recorded a low incidence of clinical changes after a positive MBD tissue sample for these patients. Again, it must be emphasized that each case involved patients with only diffuse and multifocal MBD. Patients with a recent cancer diagnosis and no distant disease, or an active cancer without known metastasis, were excluded as this group would have required a tissue diagnosis outright.

In total, there were six instances in which the clinical management changed as a direct result of a positive tissue sample. One change occurred in the form of additional imaging to help obtain a more specific origin of the primary tumor. Therefore, there may be a benefit for sending tissue in patients with carcinoma of an unknown primary. The diagnosis of a cancer origin is often difficult, and some studies suggest an

Table II. *Changes in clinical management as a result of a positive tissue sample based off lesional specimens sent during surgery for known, widespread metastatic bone disease.*

Case	Age (years)	Primary	Procedure	Description of change
1	61	Breast	Internal fixation	Patients switched from cytotoxic regimen to targeted therapy with Capecitabine.
2	76	Lung	Internal fixation	Medication switch from targeted therapy to cytotoxic agents plus targeted therapy based off tissue immunohistochemistry.
3	72	Unknown	Total hip arthroplasty	Histology from tissue received suspected sinonasal cavity origin; prompted directed management.
4	71	Prostate	Total hip arthroplasty	Patient was switched to abiraterone acetate following tissue confirmation.
5	41	Colon	Total hip arthroplasty	Patient was switched from systemic therapy to targeted Panitumumab regimen after tissue sampling.
6	23	Lymphoma	Internal fixation	Hematologic metastasis confirmed on histopathology, after which patient was started on cytotoxic agents.

increased incidence of skeletally related events in patients with a prolonged time to diagnosis (15-17). The patient in this study was initially treated with internal fixation of the humerus for a lesion consistent with adenocarcinoma of unknown origin. However, the patient eventually developed femoral, tibial, and vertebral metastasis before additional tissue during a subsequent procedure revealed possible sinonasal origin. Eventually during later surgery, the histopathology resulted in a change in management including referral and further imaging. Although anecdotal, sending tissue for diffuse metastasis of unknown primary may expediate identification of the tumor, direct medical treatment, and possibly prevent additional skeletally related events.

The other five changes after a positive tissue sample were with medication. As mentioned above, patients with an unknown primary may require additional testing. Typically, a bone biopsy in this setting reliably confirms the origin, and recent studies suggest that the rate of a positive sample following bone biopsy for an unknown primary is 97.9% (17). When the biopsy is inconclusive, however, additional tissue during surgery may be needed. We observed one patient in whom serial bone biopsies up until surgery were inconclusive. While the suspicion of the multidisciplinary group was a hematologic malignancy based off labs and imaging, lymphoma was eventually confirmed during surgery from femoral reamings and resulted in directed medical therapy. These data therefore might encourage the practice of sending tissue in the setting of known or diffuse MBD when previous biopsies are inconclusive.

Although the incidence of changes was low overall, we observed a possible role for sending tissue in select cases of breast metastasis as the receptor profile from lesional tissue may differ from that of the primary. One such change was observed in the current study, in which a positive tissue sample prompted a change from cytotoxic to targeted therapy. With respect to lung cancer, one positive sample demonstrated an immunohistochemical pattern requiring additional treatment based off a PDL-1 assay from skeletal tissue retrieved during internal fixation. Finally, the remaining two changes occurred in a patient with colon cancer who was switched to a targeted regimen after tissue revealed cecal origin, in addition to a patient with prostate cancer who was switched to abiraterone acetate based off MBD tissue assays, respectively. Ultimately, however, changes in clinical management are rare. While there may exist a possible role for sending tissue in select cases, a discussion within a multidisciplinary setting is crucial to identify patients that may benefit from additional tissue evaluation by pathology as well as identify any change in management that may arise thereafter.

Of note, the current study recorded a lower positive sample rate in reamings-only cases than for cases in which tissue was sent during resection/intralesional procedure with primary arthroplasty, endoprosthetic reconstruction, or methylcrylation. This was likely due to a lower volume of tissue obtained during reamings than resection, which was suggested by the trend towards increased likelihood of reaching a positive sample with more tissue sent. Another possible reason for low positive rate from reamings could be destruction of the tissue or dilution of the sample with normal tissue. To our knowledge, this is the first identifiable study that describes the clinical utility of sending femoral reamings, which is a common practice though has no evidenced-based data supporting its role in surgery for MBD.

As mentioned above, any patient without confirmed, multicentric MBD deserves a tissue diagnosis. Alternatively, in those cases of known multifocal MBD, a multidisciplinary discussion should take place to determine whether sending additional tissue may be helpful in the patient's care plan. Our study found that for the majority of these patients, sending tissue only increases the time and cost and often does not yield a positive sample. More importantly, however, the majority of positive samples do not lead to a change in the clinical management. It appears that following a positive sample it is very uncommon to pursue additional procedures or work-up except in select cases of breast, lung, or hematologic malignancies, and unknown primaries. Therefore, a multidisciplinary team

discussion is warranted prior to sending these additional tissues. This is important because there is no doubt that the prevalence of patients with MBD continues to increase, and cost-effective care of these patients will be a growing part of orthopedic oncology practice in the decades ahead.

This study is primarily limited by its retrospective nature. An additional though important limitation is the fact that this study was conducted within a single institution. As such, the generalizability of the results is limited, as certain treatment algorithms and indications for sending tissue during surgery for MBD may vary by institution. With respect to interpreting any change in clinical management, this study is limited by data available in the medical record. For example, medical records often do not include details on the decision-making process by medical oncologists following confirmation of MBD from skeletal tissue. While most treating oncologists likely followed the expected algorithm that they had in place prior to surgery, it was impossible to know whether changes were initially considered following a positive tissue sample of MBD. Lastly, the study mentions the financial burden of receiving and interpreting metastatic tissue from a histological perspective. Given the increasing volume of MBD patients seen routinely in clinical practice, there likely needs to be a discussion regarding the cost-effectiveness of routine histologic examination of tissue sent from patients with diffuse, known MBD. While we did not include data on cost, other studies have proposed that a routine histologic examination during orthopedic procedures is not cost-effective and often has a high rate of discordant or discrepant findings (14).

In summary, this study provides some of the first identifiable evidence of the clinical utility of sending tissue during surgical cases of diffuse, multifocal MBD. Despite the routine practice of sending tissue for histology in this setting, a change in the subsequent clinical management is rare. More often, these patients continue the same systemic treatment algorithm pre- and post-operatively.

Conflicts of Interest

None declared.

Authors' Contributions

Charles A. Gusho: Data collection, Data analysis, drafting of the initial and final article, review and editing of the final article. Alan T. Blank: review and editing of the final article.

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