Operative Management of Metastatic Melanoma in Bone May Require En Bloc Resection of Disease

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Abstract

Background Bone metastasis is a poor prognostic indicator in melanoma. Some authors have advocated only palliative treatment for patients with osseous disease.

Questions/purposes We determined (1) overall survival after surgery for bone metastasis in patients with malignant melanoma, (2) the rate of local relapse after surgery for bone metastasis, (3) whether certain patients might benefit from more extensive surgery to reduce the risk of local recurrence, and (4) whether there is an effect of prior radiation on survival and local progression.

Methods We identified 37 patients who underwent 41 orthopaedic procedures for metastatic melanoma to bone in

the pelvis or appendicular skeleton, including 20 for pathologic fracture, from our institutional orthopaedic database and performed a retrospective review of their charts and radiographs. The femur (n = 19) and humerus (n = 11) were the most common operative sites. Kaplan-Meier survivorship was used to determine overall survival and local progression-free survival.

Results The median survival from surgery was 9 months (range, 1–135 months). Kaplan-Meier analysis showed overall survival of 30% at 12 months and 17% at 24 months. Local recurrence developed in seven of 41 lesions (17%). The local progression-free survival was 87% at 12 months and 67% at 24 months. Patients for whom prior radiation failed and patients who did not have excision of osseous metastases had higher rates of local recurrence. Two patients underwent amputation for uncontrolled local progression of disease.

Conclusions Osseous metastasis from melanoma behaves aggressively. The rate of local progression is substantial, and two of 37 patients in this series required amputation for progressive disease. Despite the poor overall prognosis, local control of bone disease is an important issue, and patients may benefit from resection of osseous metastases, particularly if prior radiation has failed.

Level of Evidence Level IV, therapeutic study. See the Instructions for Authors for a complete description of levels of evidence.

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Each author certifies that his or her institution approved the human protocol for this investigation and that all investigations were conducted in conformity with ethical principles of research.

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Introduction

Disease-specific management of bone metastases has become more relevant as advances in treatment of the underlying malignancies have made longer survival a reality. Although the goals of treatment have remained constant—pain relief, mechanical stability, and preservation of mobility, the means by which the goals are attained differ for each disease. Some malignancies, such as breast cancer, have lowered risk of pathologic fracture with bisphosphonate therapy; some diseases, such as myeloma, are sensitive to radiation; and certain neoplasms, such as prostate cancer, are amenable to hormonal control.

Our impression has been that melanoma in bone behaves differently from other types of malignant disease in terms of its propensity for uncontrolled growth and invasiveness, but this has not been studied in detail, and the literature on metastatic melanoma in bone is not extensive [1, 2, 9, 10]. These previous studies have varied in the reported rates of bone metastases and recommendations for treatment. One study recommended palliative treatment only [5]. One of the key problems for surgeons is to determine whether a high risk of local relapse or progression warrants an aggressive surgical approach that may include en bloc resection of bone disease.

The goal of the current study was to evaluate the results of surgical treatment of osseous metastatic disease in malignant melanoma. The value of achieving local control, particularly in patients who may have an expectation of longer survival, warrants investigation. We determined (1) overall survival after surgery for bone metastasis in malignant melanoma, (2) the rate of local relapse of metastatic melanoma in bone, (3) whether certain patients might benefit from more extensive surgery to reduce the risk of local recurrence, and (4) whether there is an effect of prior radiation on survival and local progression.

Patients and Methods

Study Design

We performed a retrospective review of patients treated surgically for osseous lesions secondary to metastatic melanoma at one institution between 1990 and 2006. Patients were identified by querying the Department of Orthopaedic Oncology Surgical Database. Only patients who underwent operative intervention for disease in the pelvis or appendicular skeleton were included in the study. Patients with lesions of the spine or cranium were excluded. Medical records, operative reports, radiographic studies, and pathology reports were reviewed. The study

Table 1. Patient demographics

Characteristic	Value
Number of patients/procedures	37/41
Sex (number of patients)	
Male	21
Female	16
Age (years)*	51 (39–84)
Primary melanoma site (number of patients)	
Known	25
Unknown	12
Followup (months)†	6 (0–135)
Sites of metastasis (number of lesions)	
Upper extremity (n = 18)	
Clavicle	1
Scapula	1
Humerus	11
Ulna	1
Radius	2
Metacarpal	1
Phalanx	1
Lower extremity (n = 23)	
Acetabulum	1
Femur	19
Tibia	2
Calcaneus	1

* Values are expressed as mean, with range in parentheses; †values are expressed as median, with range in parentheses.

was approved by and conducted in accordance with guidelines by our institutional review board.

Patients

Thirty seven patients underwent surgery at 41 skeletal sites for metastatic melanoma to bone (Table 1). There were 21 men and 16 women, with a mean age of 51 years (range, 39–84 years). Twelve of the 37 patients (32%) did not have a known primary cutaneous tumor. Two patients presented with osseous metastasis as the first site of disease, and one of these patients had an isolated bone metastasis. All other patients had multiple metastases at the time of orthopaedic intervention, with lymph nodes being the most common site (Fig. 1). The mean number of additional sites of disease was 4.4 (range, 0–11). Twenty-eight of 37 patients (76%) experienced a new site of metastatic disease after their orthopaedic procedure (Fig. 1). Bone (n = 18) and brain (n = 12) were the most common locations for further metastasis. The median time from original diagnosis to development of bone metastasis was 26 months (range, 0–236 months).

Fig. 1 The distribution of other disease sites at the time of intervention for osseous metastasis is shown in the lower bars. After surgery, the additional sites of surgery are shown in the upper bars. The most common site of disease before surgery was the lymph node. After surgery, bone was the most common site of new metastatic disease, and this occurred in 18 of 37 patients (49%). The cell types with one bar have a missing bar value of 0.

The minimum followup was 1 month (mean, 6.1 months; range, 1–135 months). At the time of last followup, three of 37 patients were alive. The median time from last orthopaedic followup to death was 2 months (range, 0–24 months; mean, 5 months). Eleven patients had more than 6 months between last orthopaedic followup and death, and one patient was alive at 37 months without disease but stopped coming to clinic. These 12 patients were considered lost to orthopaedic followup. All deaths were secondary to disease progression. Date of patient death was determined from patient records and the Social Security Death Index.

Surgery

Twenty of 41 procedures (49%) were performed for pathologic fracture (Table 2). Four patients (11%) underwent operative intervention at two different sites of bony disease. Surgical treatment included tumor excision in 36 procedures (19 with en bloc resection and 17 with intralesional excision). In five procedures, the fracture was stabilized without tumor removal. No patient underwent preoperative selective arterial embolization of the tumor to decrease intraoperative blood loss.

Statistical Analysis

Overall survival and local progression-free survival were determined by Kaplan-Meier analysis, and the log rank test was used to compare the survival curves for different groups. Since patients with terminal cancer could not continue their followups in the orthopaedic clinic until the

Table 2. Types of surgery

Procedure	Number of procedures (total n = 41)
Tumor not removed (n = 5)	
Nail (closed)	4
Plate	1
Tumor removed (n = 36)	
Curettage (n = 17)	
Nail + polymethylmethacrylate	12
Nail	1
Plate + polymethylmethacrylate	1
Pins + polymethylmethacrylate	1
Plate + bone graft	1
THA	1
Wide resection (n = 19)	
Endoprosthesis	14
No reconstruction	3
Amputation	2

time of death, they were censored at the time of last orthopaedic followup for purposes of calculating local progression-free survival. Local progression was assessed by radiographs and MR images. An increase in the lytic area of bone or enlargement of soft tissue tumor observed on MR images was interpreted as a positive sign of local progression. Local recurrence was defined as the reappearance on imaging studies of osseous or soft tissue tumor after prior excision, and this also was scored as positive for local progression. Student's t-test was used to compare means. Linear regression for two continuous variables was determined by sum of least squares. The 95% CI is reported

where appropriate for various statistics. Statistical significance was defined as p values of 0.05 or less. No sensitivity analyses were performed. Statistical analyses were performed using IBM SPSS version 21 (Armonk, NY, USA).

Results

Survival

Overall patient survival by Kaplan-Meier analysis after surgery for bone metastasis was 30% at 1 year and 17% at 2 years. Median survival from the time of first surgery was 9 months (mean, 16 months; range, 1–35 months) (Fig. 2). At last followup, three of 37 patients were alive. The median survival was 10 months (mean, 21 months; range, 1–135 months) for patients with a known cutaneous primary versus 8 months (mean, 12 months; range, 1–64 months) for patients without a known primary ($p = 0.70$). The risk ratio for death was 3.2 (95% CI, 1–10) for patients who did not have metastatic tumor excision compared with patients who had tumor removal. Kaplan-Meier analysis showed median overall survival of 2 months with no tumor excision and 10 months with excision ($p = 0.03$). Overall survival after surgery for bone metastasis did not correlate with the time to development of bone metastasis in linear regression analysis ($p = 0.87$).

The number of sites of metastatic disease at the time of surgery did have an effect on overall survival. There was one patient who had no other disease and six patients who had only one organ system involved. In this analysis, in transit skin lesions and regional lymph nodal involvement

were considered a single organ. In Kaplan-Meier analysis, the median overall survival for the patients who had 0 or one additional organ system involvement was 21 months (95% CI, 0–43 months) as compared with 7 months (95% CI, 4–11 months) for the patients who had multiorgan metastatic disease ($p = 0.009$). Patients who had multiple osseous metastases all had multiorgan disease.

Local Recurrence

Seven of 41 lesions (17%) were complicated by local recurrence or progression of disease. The local progression-free survival was 87% (95% CI, 81%–93%) at 1 year and 67% (95% CI, 46%–89%) at 2 years. In three patients, no additional surgery was performed either because the patient was minimally symptomatic (one patient) or the intramedullary nail was still stabilized by interlocking screws above and below the tumor (two patients).

The potential role of tumor size on recurrence was determined. The mean size of the metastatic tumor as determined by preoperative imaging studies was 8.9 cm in greatest dimension for tumors that had local progression and 7.7 cm for tumors that did not progress ($p = 0.47$). The size could be determined from cross-sectional imaging using MRI or CT in 12 of 37 tumors. Conventional radiographs were used for the remaining tumors.

Four patients had surgery for local recurrence. One patient had increasing pain, fracture, and progression of disease develop 3 months after radiation and closed intramedullary fixation of the humerus (Fig. 3A–B). The recurrent tumor was resected, and the nail was converted to an intercalary endoprosthesis (Fig. 3C). Another patient underwent surgery for hemorrhage and recurrence of disease 3 months after radiation and resection of a distal ulna lesion. Two patients underwent shoulder disarticulation after massive recurrence of disease after excision of metastasis in the proximal humerus.

Surgical Excision of Metastasis

The risk ratio for local disease progression was 3.2 (95% CI, 0.4–25.6) for patients who did not have metastatic tumor excision compared with patients who had tumor excision, either by intralesional curettage or en bloc excision. Kaplan-Meier analysis showed worse local progression-free survival for patients who did not have surgical tumor extirpation ($p = 0.001$, Fig. 4). In pair-wise comparisons, curettage and en bloc excision were superior to no excision regarding local progression-free survival ($p = 0.01$ and $p = 0.001$, respectively), but there was no difference between curettage and en bloc excision ($p = 0.99$).

Fig. 2 Kaplan-Meier analysis of overall patient survival showed survival rates of 60% (95% CI, 44%–76%) at 6 months, 30% (95% CI, 15%–45%) at 1 year, and 17% (95% CI, 6%–28%) at 2 years.

Fig. 3A–C Local disease progression in a patient with an impending fracture of the mid-shaft of the humerus who underwent closed nailing without tumor removal is shown. **(A)** A postoperative radiograph shows a humeral nail and tumor erosion of the lateral cortex of bone without fracture. **(B)** A followup radiograph taken 3 months after surgery shows increasing lytic changes in bone and a new pathologic fracture, consistent with local progression of disease. **(C)** The nail was removed, and the tumor was resected en bloc. The humerus was reconstructed with a modular intercalary endoprosthesis, which remained stable until the patient's death.

Fig. 4 Kaplan-Meier analysis of local progression-free survival showed better survival when the metastatic tumor was excised versus not excised. At 6 months, local progression-free survival was 93% (95% CI, 88%–98%) for patients with tumor excision compared with 40% (95% CI, 11%–70%) for patients without tumor excision ($p = 0.033$). No patient without tumor excision survived beyond 9 months.

Prior Radiation

Ten patients had prior palliative radiation of osseous metastases fail and they underwent surgical treatment. Five patients had a pathologic fracture, two had an impending pathologic fracture attributable to progressive disease, and three experienced worsening pain. The median time from

completion of radiation to surgery for the 10 patients was 3 months (range, 0–45 months).

Three of the 10 patients had local progression of disease after surgery. Kaplan-Meier analysis showed worse overall patient survival and worse local recurrence-free survival in patients with failed prior palliative radiation (Fig. 5). The risk ratio for local disease progression in patients with failed radiation before operative intervention was 3.0 (95% CI, 0.5–19.0) compared with patients without prior radiation. There was no association between radiation and wound complications ($p = 0.61$) or nonunion of fractures ($p = 0.63$) by chi-square analysis.

Discussion

Previous studies have suggested that patients with metastatic melanoma in bone have a poor prognosis [2, 3, 10]. Because melanoma is not one of the more common types of malignancy to involve bone, there are few studies pertaining to the treatment of metastatic melanoma in bone [5, 10, 12]. Our study confirms the impression that overall survival of patients is poor after surgery for osseous metastasis and the rate of local progression of disease high. Patients who underwent conservative surgery without tumor removal almost uniformly had rapid local progression of disease. Even among patients who had undergone excision of the metastatic disease, there was a relatively high rate of local recurrence, and two patients subsequently underwent amputation for massive local recurrence. The

Fig. 5A–B Patients for whom prior palliative radiation to osseous metastases failed had worse overall survival and local progression-free survival by Kaplan-Meier analysis. **(A)** At 12 months overall survival was 43% (95% CI, 26%–62%) for patients without prior radiation compared with 11% (95% CI, 0%–32%) for patients in whom prior radiation failed ($p = 0.033$). **(B)** At 12 months local progression-free survival was 91% (95% CI, 85%–97%) for patients without prior radiation compared with 77% (95% CI, 63%–91%) for patients in whom prior radiation failed ($p = 0.097$).

results of our study suggest that metastatic melanoma to bone behaves aggressively, particularly after prior palliative radiation fails.

This study has some limitations. First, as a retrospective analysis, we could not control or determine adequately the indications for a particular type of surgery, such as curettage versus wide excision. Second, a larger number of patients would have increased the power of the study to detect small effects such as size of tumor on recurrence, but melanoma is an uncommon form of osseous metastasis,

and the accrual of patients in such a study cohort takes many years. Third, it is difficult in studies of bone metastasis to determine the outcome of surgical treatment as patients are near death, and orthopaedic followup becomes limited in the final months of life. Twelve patients were considered lost to orthopaedic followup on the basis of having more than 6 months between their last orthopaedic visit and death. Although many of the patients continued to be seen by medical oncologists at our institution, the patients potentially could have had local progression of disease. This could affect the statistical analysis of local progression-free survivorship, and our estimates should be considered best-case estimates, as patients lost to followup tend to have worse health status. However, there was only one patient considered lost to followup for purposes of determining overall survival, and the Kaplan-Meier analysis for overall survival is considered accurate on this basis. Fourth, we could not evaluate the effect of systemic treatment on local control. It seems possible that patients who are on third or fourth-line treatment have resistant disease which may make it more prone to aggressive behavior and local failure. The wide disparity in previous systemic treatments of our patients makes analysis of this beyond the scope of our current study. However, the effect of systemic treatment may become increasingly important for melanoma, given the advent of new treatment paradigms for the disease, and the results of the current retrospective study must be viewed in this context [6]. Some of the most exciting developments in oncology in recent years pertain to new targeted therapy and immunotherapy for melanoma. Patients with specific mutations in BRAF are now candidates for treatment with agents such as dabrafenib [4]. Using a completely different strategy, researchers also have found that blocking the cytotoxic T lymphocyte antigen 4 (CTLA4) receptor [8] and the programmed cell death 1 receptor (PD1) [11] on activated T lymphocytes can reverse a tumor-induced suppression of lymphocytes and thereby induce a potent immune response against the cancer [7].

Regarding our first question pertaining to overall survival after surgery, our study corroborates the previous finding that metastatic melanoma to bone carries a grave prognosis [2], and 70% of our patients had survival less than a year. In our patient cohort, the median overall survival was 9 months after the first surgery for osseous metastasis. Wedin et al. [12] had similar findings but with an even shorter median survival of 1.9 months after surgery. Similarly, Barth et al. [2] described poor life expectancy in patients with metastasis to bone, whose survival was similar to that of patients with liver and brain metastasis. It is possible that short survival may be related in part to bone metastasis being a late finding in most patients with metastatic melanoma. Most patients in our

series (30 of 37) had disease that affected multiple organs at the time osseous metastases were detected. However, survival was not uniformly poor for all patients, and one of our patients has been continuously free of disease for more than 10 years after finishing treatment for metastasis in bone, brain, lung, and other organs. Autopsy studies show that melanoma may be more common in bone than generally thought. Selby et al. [9] reported that approximately 50% of patients had bone metastasis, with most being subclinically present in flat bones. Other studies have reported a lower rate of bone metastasis from melanoma, possibly because not all lesions are symptomatic. Stewart et al. [10] found 6.9% of patients with metastatic melanoma had bone metastasis, which occurred predominantly in flat bones and axial sites. Balch et al. [1] reported that 17% of patients had bony involvement. They found that patients who presented solely with osseous metastases did not have better survival than patients with nonosseous metastasis [1].

Our second question was to determine the rate of relapse after surgery for osseous metastasis. We found that there was a relatively high rate of local relapse, and the local progression-free survival was estimated to be 67% at 2 years after surgery. As mentioned previously, because of incomplete orthopaedic followup, this is likely to be an underestimate of the true problem. However, in certain cases, such as statically interlocked intramedullary nailing, the reconstruction may remain stable for the duration of the patient's life. More work is needed to define what proportion of cases of local progression is clinically significant with respect to pain, instability, and loss of function.

Our third question was whether certain patients may benefit from more extensive surgery to reduce the risk of local recurrence. We found that removal of tumor, either by intralesional curettage or en bloc resection, was associated with better local progression-free survival, but there was no statistical difference between curettage and en bloc resection. These results need to be interpreted cautiously, and one should not immediately conclude that curettage and en bloc resection were equivalent, as there may have been selection bias regarding which patients underwent en bloc resection. Our results contrast with those of previous studies, which have differed in their recommendations for surgical treatment of osseous metastasis in melanoma. Initial reports on surgical management of melanoma suggested a limited role for surgery in disseminated cases. One study of 11 patients reported a mean survival less than 6 months, and the authors favored palliative treatment only [5]. Stewart et al. [10] recommended that operative intervention be limited to patients with unstable pathologic fractures and stated that prophylactic long-bone fixation was rarely indicated. However, resection of isolated bony

metastases in the appendicular skeleton was advocated by DeBoer et al. [3], who reported improved survival characteristics, especially when bone lesions were identified after a prolonged latency period (> 2 years) [3]. Although it may seem appropriate that patients who have limited expected lifespans should receive conservative treatment, our study shows that there is considerable morbidity for patients who have uncontrolled tumor growth at metastatic osseous sites. The fact that two patients underwent amputation for extensive local recurrence reinforces the idea of maintaining local control in this disease. In trying to determine which patients might be suitable candidates for en bloc resection, we note that overall survival was better for the patients who had no other sites of disease or only one organ system involved at the time of surgery for bone metastasis. Local relapse for these patients who live longer may be more problematic than for patients with multiorgan involvement and short life expectancy. The shorter overall survival for patients who did not undergo tumor excision was likely the result of selection bias. Patients who were very debilitated from advanced disease would have been more likely to undergo simple closed nailing of pathologic fractures.

Our fourth question was whether prior radiation affected survival and local control. We found worse overall survival and increased likelihood of local progression in patients whose local disease had progressed after prior palliative radiation. These patients may have had a resistant disease process. Even though overall survival in this radiation-refractory group was worse, two of 10 patients were alive nearly 5 years after surgery. These two patients underscore the importance of adequate surgical treatment of metastases, which should not be minimized simply because a patient is perceived to have a poor prognosis. One could make the argument that en bloc resection needs to be considered more strongly for the patients in whom prior radiation failed.

The development of osseous metastases from malignant melanoma was associated with poor patient survival and prognosis. Although 70% of patients died in a year, some patients with multiple metastases lived well beyond 2 years. Metastatic melanoma in bone tends to behave aggressively, especially in patients with failed prior palliative radiation. Excision of tumor at the time of surgery for osseous metastases resulted in better local control and should be considered to avoid the morbidity of local disease progression. However, for the present time, it must be left to the surgeon's judgment regarding which patient should undergo en bloc tumor resection. More work is needed to identify the factors that will determine which patients will survive longer and have greater need for local control and a durable orthopaedic construct.

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