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Preliminary analysis of distinct clinical and biologic features of bone metastases in melanoma

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Abstract

Melanoma disseminates to the skeletal system where it is then difficult to treat. Yet there remains limited research investigating metastatic bone disease (MBD) in melanoma. Here, we evaluate whether there are distinct clinicopathologic variables at the time of primary melanoma diagnosis that predispose metastases to engraft bone, and we test the hypothesis that patients with MBD have different responses to treatment. Cutaneous melanoma patients enrolled in a prospective database were studied. Individuals with metastatic melanoma and bone metastases (M-Bone) were compared to those with metastatic disease but no M-Bone. 198/463 (42.7%) with unresectable metastatic melanoma had M-Bone and 98 developed bone mets as first site. Progression free and overall survival were significantly worse in patients with M-Bone compared to those without M-Bone ($p < 0.001$) independent of treatment modalities, and in patients whose melanoma spread to bone first, compared to those who developed first mets elsewhere ($p < 0.001$). Interestingly, patients with bone mets presented with primary tumors that had more tumor infiltrating lymphocytes (TIL) ($p < 0.001$) and less often a nodular histologic subtype compared to patients without M-Bone ($p < 0.001$). Our data suggest that melanoma bone metastasis is a distinct clinical and biological entity that cannot be explained by generalized metastatic phenotype in all patients. The observed dichotomy between more favorable primary histopathologic characteristics and a grave overall prognosis requires more studies to elucidate the molecular processes by which melanomas

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infiltrate bone and to build a mechanistic understanding of how melanoma bone metastases yield such detrimental outcomes.

Keywords

Metastatic melanoma; Bone metastasis; Overall survival; Treatment response; Bone directed therapy

Introduction

An estimated 5–20% of patients with melanoma develop metastatic bone disease (MBD) during the course of their illness.^{1–3} These are usually osteolytic lesions that negatively impact morbidity and mortality. Specifically, the infiltration of bone with metastatic melanoma cells puts patients at increased risk of skeletal related events (SREs) including pathologic fractures, hypercalcemia, and/or severe pain requiring palliative radiation.^{2–7} Emerging therapies for advanced melanoma have led to improved survival outcomes, but patients remain at high long-term risk for developing distant metastases.^{8–16}

Metastatic organotropism is increasingly viewed as a non-random phenomenon. Metastatic organotropism refers to the biological phenomenon whereby a tumor typically or preferentially metastasizes to certain sites. Melanoma tends to metastasize to liver, brain, and lung.^{17–21} Skeletal tissue has already been identified as a preferential target in certain cases of lung, breast, and prostate cancer, which challenges the conventional paradigm of MBD as a manifestation of the generalized metastatic phenotype.²² To our knowledge, no studies have investigated whether distinct clinicopathologic variables predispose melanomas to engraft bone, or whether MBD itself yields unique clinical outcomes compared to metastatic disease without bone involvement. As the incidence of bone metastases increases, it is imperative to close this knowledge gap in order to improve risk stratification, guide surveillance protocols, and facilitate early intervention.

In this study, we investigated melanoma bone metastases in a cohort of patients with prospective protocol driven follow up. We first analyzed a series of demographic, clinical, and pathological factors in patients who developed melanoma with bone metastasis (M-Bone) and those who developed metastatic disease but no M-Bone. We then tested the postulate that patients with M-Bone and without M-Bone have distinct clinical outcomes including response to specific treatments as well as overall morbidity and mortality.

Material and Methods:

Patient Population:

The patient population was drawn from a cohort of individuals who were treated at The Laura and Isaac Perlmutter Cancer Center at NYU Langone Health between 2002 and 2017. All of the patients in the cohort were enrolled into an IRB approved institutional database (#10362) and had prospective-driven follow-up. Informed consent was obtained at the time of enrollment. Patients who ultimately developed unresectable metastatic melanoma were included in this analysis.

Data Analyses:

This cohort of patients who developed unresectable metastatic melanoma was divided into two groups: those with metastatic disease with M-Bone and those with metastatic disease without M-Bone. The two groups were compared in terms of the patients' biographic, demographic, and treatment information. Pathologic, histologic, molecular, and anatomic features of the primary melanoma were also compared between groups. This included the presence or absence of ulceration and tumor infiltrating lymphocytes (TILs) as well as the mitotic index, histologic subtype, and mutation status of *BRAF* and *NRAS*. Mitotic index was defined as absent = 0, few = 1, moderate = 2–10, and many > 10 mitoses. In patients with M-Bone, the location of bone lesions and the incidence of skeletal related events were both determined. SREs were defined as pathologic fractures, hypercalcemia, and treatment with radiation therapy or surgical resection. The difference in progression free survival (PFS) and overall survival (OS) was compared between patients with and without M-Bone. PFS was defined as the time from treatment initiation until the time of disease progression or death, whichever occurred first. Bone specific PFS was defined as the time from treatment initiation until bone disease progression or new bone metastases. OS was defined as the time of treatment initiation until the time of death.

Statistical Analysis:

The chi-square test was used to compare categorical variables in patients with M-bone versus those without M-Bone. The log-rank test was performed to analyze PFS and OS in the two cohorts. Kaplan-Meier curves were generated to illustrate the differences in PFS and OS between the two groups. A multivariable evaluation of risk factors was performed using Cox proportional hazard models. The adjusted prognostic factors in the multivariable models included performance score, number of metastatic sites, and elevated lactate dehydrogenase (LDH). The results are presented as adjusted hazard ratios (HRs) with 95% confidence intervals (CIs). The proportional hazard assumption was checked using graphical diagnostics based on the scaled Schoenfeld residuals. All statistical tests were two-sided. The threshold for statistical significance was set at $p < 0.05$.

Results:

Patients with metastatic melanoma and M-Bone have distinct baseline characteristics compared to those without M-Bone

Table 1 illustrates the demographic characteristics of the patient population as well as the clinical, histological, and pathologic features of their primary disease. There was a total of 463 patients who ultimately developed unresectable metastatic melanoma during follow up. Of those patients, 198 patients had M-Bone and the remaining 265 patients had metastatic disease with no M-Bone. Imaging modalities used to identify metastatic disease, including bone metastases included CT, MRI and PET scans. There was a wide range in the number of bone metastases for each patient, ranging from 1–9 bone lesions. Patients who developed M-Bone had more advanced disease at the time of initial diagnosis (27/198; 14%) compared to patients without M-Bone (11/265; 4%; $p = 0.005$). In patients with M-Bone, the primary tumor was more frequently located in axial tissue (99/198; 58%), which includes clavicle, scapula, sternum, trunk, and pelvis; while in patients without M-Bone, the primary

melanoma more often originated from the extremities or head and neck (171/265; 65%; $p<0.001$). Interestingly, nodular melanoma, an aggressive histologic subtype was less common, 34% (67/198) in patients with M-Bone had compared to 57% (150/265) of patients with no M-Bone ($p<0.001$). In addition, primary tumors in patients who developed M-bone have more tumor infiltrating lymphocytes (TIL) ($p<0.001$). There were no significant differences in the *BRAF* and *NRAS* mutation status of the primary lesion.

Patients with melanoma that metastasizes to bone first have worse survival compared to those whose first site of metastases was not bone

In 98/181 (54%) patients with M-Bone, bone was the first site of metastatic disease (Table 2). There was a significant difference in the survival outcomes of these patients compared to those whose first site of metastasis was elsewhere. For patients whose first metastasis was to bone, the median PFS (mPFS) was 2.7 months; patients whose first metastasis was to another location had a mPFS of 5.1 months ($p<0.001$; Figure 1A). The individuals who first metastasized to bone had a median OS (mOS) of 6.8 months and those who first metastasized elsewhere had a mOS of 13.7 months ($p<0.001$; Figure 1D). These findings held true when comparing groups based on the specific treatment types. In patients who received immunotherapy, the mOS was 10.6 months in those who first metastasized to bone and it was 21.7 months in patients whose first site of metastasis was not bone ($p=0.003$; Figure 1E). In patients treated with BRAF targeted therapy, bone as the first site of metastatic disease correlated with worse mOS compared to those who did not metastasize to bone first (7.5 months vs 10.8 months; $p=0.04$; Figure 1F).

Patients with melanoma and M-Bone had worse survival outcomes than patients without M-Bone, independent of treatment type

At the time of this analysis, 350/463 (76%) of patients included in the study had died: 160/198 (81%) patients with M-bone as compared to 190/265 (72%) without M-Bone ($p=0.03$) (Table 1). Significant differences were observed in the PFS and OS of patients with and without M-Bone. The median PFS (mPFS) was 3.9 months in patients with M-bone compared to 5.3 months in patients without M-bone ($p=0.008$; Figure 2A). However, when stratified based on individual treatment regimens, there were no differences observed in the PFS between groups (Figure 2B and 2C), although there was a trend towards worse PFS in patients with M-bone who received BRAF targeted therapy (Figure 2C). The median OS (mOS) was 9.0 months in patients with M-Bone and 23.0 months patients without M-Bone ($p<0.001$; Figure 2D). This finding was independent of systemic treatment. When stratified based on treatment regimens, there was a significant difference in the OS of patients treated with BRAF targeted therapy. The mOS of patients with M-Bone who received BRAF targeted treatment was 10.3 months; the mOS of patients without M-Bone was 22.0 months ($p=0.03$; Figure 2F). There were no differences in the OS of patients with and without M-bone when treated with immunotherapy ($p=0.066$; Figure 2E).

The univariate analyses revealed that patients with M-bone have worse PFS than patients without M-bone, independent of the type of systemic treatment ($HR=1.30$; $p=0.009$; Table 3). However, there was no significant difference between the PFS of both groups when stratified based on specific type of systemic treatment. Multivariable analysis demonstrated

that patients with M-bone had worse OS regardless of the type of systemic treatment received and independent of performance status (PS), number of metastatic sites, and LDH (HR=1.38; p=0.047). Patients with M-Bone who received targeted therapy had worse OS as compared to those without M-Bone (HR=1.96; p=0.048). There was no statistically significant difference in the OS of patients when treated with immunotherapy (HR=1.11; p=0.61). In multivariable analyses, performance status, number of metastatic sites, and elevated LDH all independently predicted for worse OS in patients with M-Bone compared to those without M-Bone (HR=1.82; p<0.001; HR 1.06; p=0.02; HR=1.62; p<0.001, respectively).

Bone lesions corresponded with substantial morbidity, but bone directed therapy did not improve PFS

In the group of patients with M-Bone, most bone lesions occurred in the axial skeleton. This applies to both the time of initial bone metastases (243/339; 72%) and over the course of disease progression (314/468; 76%; Table 2). In terms of SREs, 53/170 (31%) patients received radiation therapy to bone metastases. There were 49 (26%) patients who experienced a pathologic fracture and 16 (8%) patients who experienced multiple fractures. There were 21/169 (12%) patients who underwent orthopedic surgery for treatment of their bone lesion. Although 5/83 patients had elevated serum calcium levels, the level was unknown for the remaining 110 patients. Only 40/198 (24%) patients received bone directed therapy, and for those who did, the bone directed treatment did not change bone specific PFS compared to those who did not receive bone directed treatment (p=0.14; Figure 3). At the time of this analysis, survival was less than 50% for both of those groups.

Discussion:

In this study of prospectively-enrolled patients with unresectable melanoma, we report that metastases to the bone were quite common. Approximately 43% of patients with metastatic melanoma had M-Bone. Although there is limited data for comparison, this incidence is higher than previously reported by Zekri et al, who found that only 17.2% of those with metastatic disease had bone lesions.³ The discrepancy could be accounted for by differences between our cohorts including the fact their study period was from 2000 until 2008 whereas ours was from 2002 until 2017. Treatment advances in the past decade have led to improved life expectancy for patients with melanoma.¹⁷⁻²¹ Many individuals now survive long enough to develop metastases and this alone could account for the difference in our observations. It also speaks to the need for more contemporary studies of patients with MBD who were treated in the era of targeted agents and immunotherapy. The treatment landscape for advanced melanoma, defined as unresectable and metastatic melanoma, has changed so much since 2011 that follow up studies investigating bone metastases should include cohorts from this contemporary treatment era, as opposed to previous studies with cohorts predating newer treatment modalities including immune checkpoint inhibitors and targeted therapy.

We observed that most patients with MBD had their initial bone metastasis in the axial skeleton instead of the extremities. The most common sites of bone metastases were the vertebrae, pelvis, femur, and humerus, a pattern which mirrors that seen in preclinical, *in*

vivo mouse models of melanoma, established using the B16 malignant melanoma cells.^{23,24} In those patients who developed multiple bone lesions, the distribution again favored the axial skeleton and not the extremities. These findings are consistent with prior findings that approximately 70–80% of patients with MBD had lesions in the axial skeleton.^{1,3,25} Interestingly, we also found that patients with M-Bone more often had a primary axial melanoma. Proximity alone is unlikely to account for this pattern of distribution. In adults, the axial skeleton is composed of red marrow, which is highly vascularized and rich in nutrition. Previous studies in breast cancer suggested that cancer cells interact with this microenvironment in order to survive and grow.^{26,27} In several preclinical studies of melanoma mouse models, cells have been observed to preferentially metastasize to the hematopoietic bone marrow.^{23,24,28} However, there is otherwise limited data on melanoma cells, which necessitates future studies and research to provide more insight into these observations.

Our data demonstrate that melanoma metastatic to the bone confers a grave overall prognosis. The mPFS in patients with M-Bone was 3.9 months and the mOS was 9 months. While these are clearly dismal survival outcomes, they are longer than what was reported in older studies. In 1981, Fon et al reported on 50 patients who had a mean overall survival time of 4.7 months once their skeletal metastasis was diagnosed.¹ In a group of 133 patients with melanoma metastatic to the spine, Gokaslan et al (2000) found that the median survival was only 4 months.²⁹ Multiple other studies have described mOS ranging around 4 months, but these all pre-dated contemporary treatment regimens.^{2–4} Patients in our cohort survived around twice as long as those in prior studies, which again highlights the recent progress in systemic therapies^{8–17}.

Although survival trends appear to be improving across all patients with metastatic melanoma, our results indicate that patients with M-Bone fare significantly worse than their counterparts without M-Bone (mOS: 9.0 months versus 23.0 months, respectively $P < 0.001$). This was despite the fact that patients with MBD were less likely to have a primary nodular melanoma and had more TILs in their primary lesion. The presence of TILs is thought to signify a host immune response mounted against malignant cells and is therefore considered a good prognostic indicator. In fact, decreased TIL intensity has been associated with worse disease free and overall survival.³⁰ Thus, we found that patients with M-Bone had worse mortality despite more favorable histopathologic characteristics of their primary tumors. We additionally found that patients whose first site of metastasis was to bone had worse mOS than those whose first metastatic lesion was elsewhere (6.8 months versus 13.7 months, respectively). However, there were no other significant clinicopathologic differences between the two groups in our analyses. This does not preclude the possibility that bone as a first site of metastatic disease is a distinct clinical entity. Future studies will need to evaluate other clinical, histologic, pathologic, and molecular differences between patients whose first site of metastases is to bone compared to those who first metastasize elsewhere.

Patients with melanoma bone disease frequently suffer from SREs. In our study, we found that 21% of patients with MBD developed a skeletal related event. Radiation therapy to the bone (31%) was the most common, followed by pathologic fractures (26%), and then surgical resection (21%). These trends are comparable to prior findings, but the overall

incidence of SREs was lower in our cohort as compared to others'. Zekri *et. al* showed that 66.3% of 89 patients with MBD experienced one or more SRE.³ More specifically, 51% of patients in their study received radiotherapy, 23% were diagnosed with hypercalcemia, 19% developed bone fractures, and 14% required surgery. The largest differences between our findings and theirs was the number of patients who received radiotherapy and the incidence of hypercalcemia. Only 5/88 (6%) patients in our study were diagnosed with high calcium levels. The lower proportion in our study is difficult to interpret because calcium levels were only reported in 88 cases and remained unknown in the remaining 110 cases. Moreover, calcium levels were only available at the time of diagnosis, so we were unable to assess whether patients developed hypercalcemia later in their clinical course. Despite these limitations, our findings regarding SREs confirm prior reports that bone metastases can have a considerable impact on patients' quality of life.

There is an ongoing debate over how to manage melanoma bone metastases and concomitant SREs. This is rooted in an incongruity between our current understanding of the molecular mechanisms of bone destruction and the lack of efficacy of medications that target those pathways. Melanoma cells induce bone damage in at least two ways. First, as has been shown in preclinical mouse models of melanoma, they secrete osteoclastogenic factors, which activate osteoclasts.^{28,31} The subsequent osteolytic bone destruction releases growth factors stored in the mineralized matrix. This further stimulates tumorigenesis and thus begins a feed-forward cycle of tumor growth and metastatic bone destruction. Second, tumor associated macrophages (TAMs) can differentiate into osteoclasts through both RANKL-dependent and RANKL-independent mechanisms, and from there induce osteolytic bone damage.³²⁻³⁴ Since the final common pathway is osteoclast activation, it is reasonable to consider treatment with bisphosphonates, which inhibit osteoclast-mediated bone resorption. Zoledronic acid was shown to reduce bone tumor burden in *in vivo* models of melanoma.³⁵ Laggner et al reported on a case of regression of bone metastases after systemic bisphosphonate treatment.³⁶ However, in our study, we found that patients treated with bone-directed therapy did not have delayed bone specific PFS.

In conclusion, we found that patients with melanoma and metastatic bone disease suffer poor morbidity and mortality. In order to improve patient outcomes, it will be imperative to identify the molecular mechanisms of melanoma bone invasion, metastatic growth, and resistance to different treatment regimens. This will facilitate the development of a consensus approach to managing patients with melanoma and M-Bone.

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Figure 1.

Patients with melanoma that metastasizes to bone first have worse survival compare to those whose disease first metastasizes to non-bone sites. PFS since (A) systemic treatment initiation ($P=3e-05$), (B) immunotherapy initiation ($P=0.1$), and (C) targeted therapy initiation ($P=0.11$). OS since (D) systemic treatment initiation ($P=8.7e-09$), (E) immunotherapy initiation ($P=0.003$), and (F) targeted therapy initiation ($P=0.041$).

Figure 2.

Patients with melanoma and M-Bone had worse survival outcomes than patients without M-Bone, independent of treatment type. PFS since (A) systemic treatment initiation (P=0.0079), (B) immunotherapy initiation (P=0.85), and (C) targeted therapy initiation (P=0.13). OS since (D) systemic treatment initiation (P= 6.4e-07), (E) immunotherapy initiation (P=0.066), and (F) targeted therapy initiation (P=0.029). Bone – patients with bone metastases. Control – patients without bone metastases.

Bone specific PFS since treatment initiation

P = 0.138

Figure 3. Bone directed therapy did not improve PFS. Bone specific PFS since treatment initiation (P=0.138).

Table 1.

Baseline characteristics and survival status of patients with unresectable stage III and stage IV melanoma with and without bone metastases.

		M-Bone	No M-Bone	P-value
N		198	265	
Gender [N (%)]	F	67 (34)	101 (38)	0.396
	M	131 (66)	164 (62)	
Ulceration	Absent	74 (49)	123 (48)	0.924
	Present	78 (51)	135 (52)	
	Unknown	46 (–)	7 (–)	
Mitotic Index	Absent	21 (15)	29 (12)	0.47
	Few	33 (24)	51 (20)	
	Moderate	34 (25)	65 (26)	
	Many	49 (36)	106 (42)	
	Unknown	61 (–)	14 (–)	
Stage at Initial Diagnosis	MIS	0 (0)	1 (0)	0.005
	I	47 (24)	67 (25)	
	II	44 (22)	74 (28)	
	III	78 (40)	111 (42)	
	IV	27 (14)	11 (4)	
	Unknown	2 (–)	1 (–)	
Histological Subtype	Acral Lentiginous Melanoma	10 (5)	29 (11)	<0.001
	Superficial Spreading Melanoma	45 (23)	75 (28)	
	Nodular Melanoma	67 (34)	150 (57)	
	Other	76 (38)	11 (4)	
Anatomic Site	Axial	99 (58)	94 (35)	<0.001
	Extremity	63 (37)	119 (45)	
	Head and Neck	10 (6)	52 (20)	
	Unknown	26 (–)	0 (–)	
TIL	Absent	24 (26)	69 (50)	<0.001
	Present	69 (74)	70 (50)	
	Unknown	105 (–)	126 (–)	
BRAF	Mut	80 (49)	101 (50)	0.953
	WT	82 (51)	100 (50)	
	Unknown	36 (–)	64 (–)	
NRAS	Mut	21 (21)	43 (27)	0.386
	WT	79 (79)	119 (73)	
	Unknown	98 (–)	103 (–)	
Status	Alive	38 (19)	75 (28)	0.051
	Died	160 (81)	190 (72)	

	M-Bone	No M-Bone	P-value
Age at Diagnosis [Median (25%, 75%)]	60.5 (45.9, 69.9)	63.8 (48, 73)	0.051
Thickness [mm, Median (25%, 75%)]	2.5 (1.1, 5)	2.7 (1.5, 5)	0.438
Follow up Month [Median (25%, 75%)]	76.4 (38.1, 151.5)	76 (41.3, 107.4)	0.796

Table 2.

Characteristics of bone metastases in patients with unresectable stage III and stage IV melanoma.

			N (%)
Bone as the first site of metastasis	Yes		98 (54)
	No		83 (46)
	Unknown		17 (–)
Bone as the only site of metastasis	Yes		3 (2)
	No		179 (98)
	Unknown		16 (–)
Site of Initial Bone Metastasis (N = 179)	Axial	Sternum	15 (6)
		Ribs	43 (18)
		Vertebral Column	113 (47)
		Pelvis	72 (30)
	Extremity	Skull	7 (7)
		Femur	41 (43)
		Humerus	24 (25)
		Other Lower Extremity	6 (6)
		Other Upper Extremity	18 (19)
Site of Overall Bone Metastasis (N = 183)	Axial	Sternum	20 (6)
		Ribs	70 (22)
		Vertebral Column	133 (42)
		Pelvis	91 (29)
	Extremity	Skull	22 (14)
		Femur	65 (42)
		Humerus	42 (27)
		Other Lower Extremity	7 (5)
		Other Upper Extremity	18 (12)
Bone Metastasis Resection	Yes		21 (12)
	No		148 (88)
	Unknown		29 (–)
Radiation Therapy to Bone Metastasis	Yes		53 (31)
	No		117 (69)
	Unknown		28 (–)
Bone Medication	Yes		40 (24)
	No		130 (76)
	Unknown		28 (–)
Calcium Level at Bone Met Diagnosis	High		5 (6)
	Normal		83 (94)
	Unknown		110 (–)
Pathological Fracture	Yes		49 (26)

		N (%)
	No	138 (74)
	Unknown	11 (-)

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Table 3.

Cox's proportional hazard models for bone metastasis and other known prognostics factors.

		PFS Overall		PFS Immunotherapy		PFS Targeted Therapy	
		HR	P	HR	P	HR	P
Univariable	Bone Metastasis	1.30	0.009	1.01	0.933	1.41	0.129
Multivariable	Performance Status	1.34	0.001	1.38	0.009	1.04	0.825
	Number of Metastatic Sites	1.00	0.906	0.97	0.306	1.08	0.094
	High LDH	1.74	<0.001	1.52	0.018	1.49	0.179
		OS Overall		OS Immunotherapy		OS Targeted Therapy	
		HR	P	HR	P	HR	P
Univariable	Bone Metastasis	1.81	<0.001	1.34	0.067	1.77	0.031
Multivariable	Bone Metastasis	1.38	0.047	1.11	0.611	1.96	0.048
	Performance Status	1.82	<0.001	1.98	<0.001	1.38	0.060
	Number of Metastatic Sites	1.06	0.017	1.04	0.236	1.09	0.091
	High LDH	1.62	0.003	1.55	0.041	1.33	0.354