Radiol Oncol 2001; 35(3): 209-14.

Bone metastases from malignant melanoma: a retrospective review and analysis of 28 cases

Elias Brountzos[1], Irene Panagiotou[2], Dimitrios Bafaloukos[2], Dimitrios Kelekis[1]

[1]Second Department of Radiology, Medical School, Athens University, Eugenidion Hospital, Athens, Greece, [2]Second Department of Oncology, Metaxa Cancer Hospital, Piraeus, Greece

Background. *The aim of the study was to evaluate the clinical characteristics, the radiological findings, and the treatment effect on the patients with bone metastases from malignant melanoma.*

Patients and methods. *Retrospective review of 293 stage IV melanoma patients during a 15-year period was made.*

Results. *Twenty-eight patients (9.5%) with bone metastases were identified; all patients had a thick or intermediate primary melanoma (Breslow 2.7-9.9). Most of the patients presented with multiple (95.6%), symptomatic (92.6%) skeletal lesions. Imaging depicted 90 bone lesions. Axial metastases were more common (86%); 54% of them were located at the spine. Skeletal radionuclide scintigraphy was non-specific; radiographij and computed tomography was diagnostic. Typical bone metastases were osteolytic (92.5%). Sixty-six lesions were treated with radiotherapy; in 79%there was a palliative response. There was no correlation between total dose or fraction size and effective palliation. The skeletal lesions did not respond to concurrent chemotherapy and/or biphosphonates. Median response duration to treatment was estimated to 2.6 months and median survival to 4.7 months.*

Conclusions. *Osseous metastases from malignant melanoma occur in the patients with more advanced primary lesions. They are most frequently osteolytic and located in the axial skeleton. Radiographij and computed tomography is diagnostic. Radiotherapy still remains the treatment of choice.*

Key words: bone neoplasms; malignant melanoma, bone metastases; imaging; radiotherapy

Received: 18 June 2001
Accepted 21 June 2001

Correspondence to: Elias Brountzos, MD, Second Department of Radiology, Medical School, Athens University, Eugenidion Hospital, 20 Papadiamantopoulou st, Athens 11528, Greece; Phone: +301 7227488; Fax: +301 729 2280; E-mail: ebrountz@cc.uoa.gr

Introduction

In most clinical series bone metastases from malignant melanoma are less frequent, ranging from 11%-17%.[1] Nevertheless, the autopsy series have revealed that skeletal involvement is more common (23-49%).[2-4]

Skeletal metastases generally occur in patients with widespread metastatic disease and usually represent a late site of recur-

rence.[5] Median survival is estimated to 2-6 months.[1-5]

The aim of our study was to present our experience concerning this uncommon site of melanoma dissemination. We retrospectively evaluated the clinical course, the radiological abnormalities and the response to treatment in this subgroup of melanoma patients.

Patients and methods

We reviewed the records of all patients with stage IV malignant melanoma treated in the 2nd Department of Medical Oncology in Metaxa Cancer Hospital from 1985 to 2000. We recorded the patients with disseminated bone disease. The inclusion data were the following: age, sex, location and thickness of primary tumor, time interval between primary tumor and bone metastases, distribution of metastases, location of the metastatic lesion, and presenting signs and symptoms.

Table 1. Characteristics of our patients' population

Age at AJCC stage IV diagnosis, years (Median, range)	50, 26 - 86
Male (%)	59
Female (%)	41
Site of primary melanoma (%)	
Lower extremity	14.1
Upper extremity	11.1
Trunk	33.3
Head & neck	37.8
Unknown origin	3.7
Breslow's thickness, mm (Median, range)	4.1, 2.7 - 9.9
Stage III diagnosed prior to stage IV (%)	70
Adjuvant treatment before stage IV (%)	22.2
Disease free interval before stage IV, months (median, range)	37, 0 - 267
Bone metastases as sole & initial site (%)	3.7
Multiple bone metastases (%)	95.6

X-ray, computed tomography, magnetic resonance and bone scintigraphy images, detecting all radiological abnormalities, were carefully reviewed. The type and response to treatment were clinically and radiologically evaluated. Effective palliation was clinically defined as significant relief from symptoms for at least 1 month. Palliative responses to radiotherapy were correlated with total radiation dose and fraction size. Survival was defined as the number of months between the diagnosis of bone metastases and death or last follow-up.

Statistical analysis was performed using the chi-squared test for the correlation between primary melanoma's thickness and the development of bone metastases. In the comparison, statistical significance was determined using a p-value level of 0.001.

Results

From a total of 293 patients with stage IV malignant melanoma, 28 patients (9.5%) with skeletal metastases were identified. The disease dissemination was diagnosed in all 293 patients using computed tomography of the chest and/or abdomen: all patients were submitted to computed tomography during regular follow-up or were evaluated with computed tomography when they became symptomatic. Table 1 shows the 28 patients' characteristics.

All our patients' primary melanomas were thick or intermediate (Breslow's thickness ranging from 2.7-9.9). From the 293 stage IV patients, 165 had a thick or intermediate primary melanoma. When correlated, statistical significance was found ($p<0.001$). Additionally, most patients (70%) had AJCC stage III disease before the diagnosis of bone metastases.

Twenty-six patients presented with symptoms of bone metastases at the time of the diagnosis: bone pain (85.1%), pathologic frac-

tures (14.8%) and/or bone marrow infiltration (7.4%) were the most common findings. Four patients (14.8%) presented with hypercalcaemia. There were no compression fractures or neurological symptoms. Only 2 patients (7.4%) were asymptomatic; in these patients, skeletal involvement was found during routine abdominal computed tomography.

In all 28 patients, thoracic and/or abdominal computed tomography was initially performed, followed by skeletal radionuclide scintigraphy in the 26 symptomatic patients, and skeletal survey radiographs in 14. Computed tomography of the appendicular skeleton was performed in 9 symptomatic patients, and MRI of the painful skeletal site in 5 patients. All studies yielded positive results.

A total of 90 metastatic bone lesions were depicted.

Table 2 shows the distribution of the lesions: axial metastases were more common (86%) than appendicular bone metastases; the lesions were located more commonly at the spine, particularly at the thoracic and lumbar vertebrae.

Table 3 demonstrates the radiological features found in radiographs and computed tomography. More than 90% of the lesions were osteolytic. A mixed osteolytic-osteoblastic pattern was uncommon (Figure 1). We found

Table 2. Skeletal distribution of the lesions

Location	Percentage of lesions (%)
Spine	54
Pelvis	21
Ribs	11
Femur & tibia	7
Humeral, ulna & clavicle	4
Temporal, maxilla & mandible	3

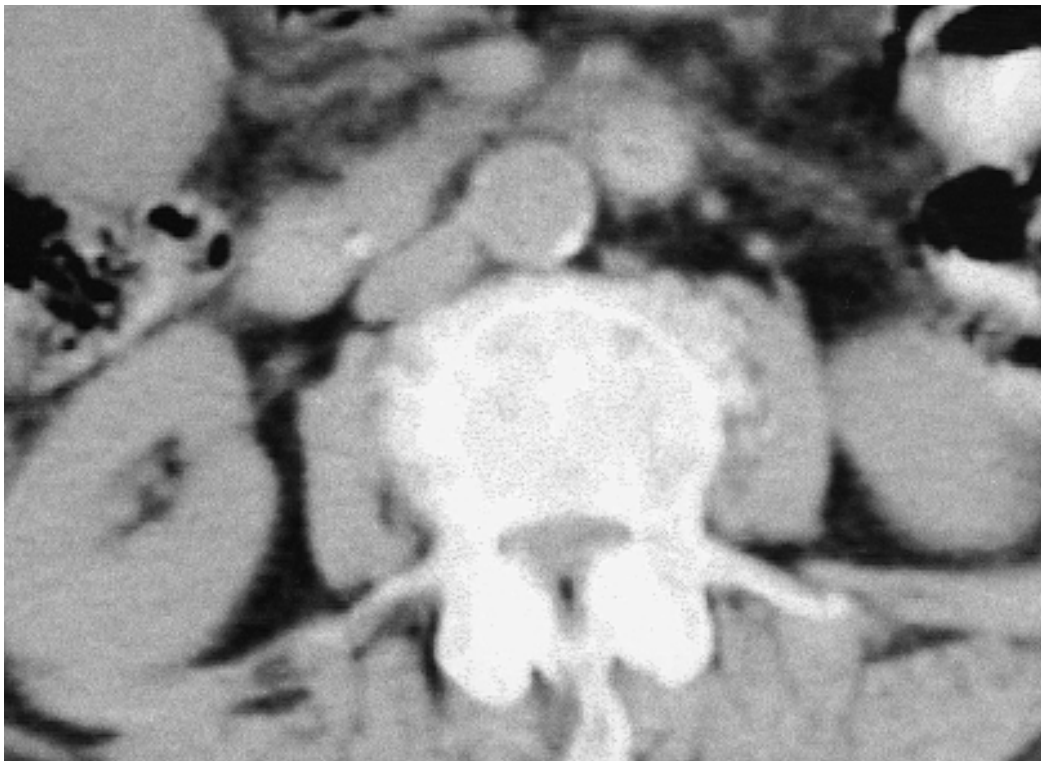

Figure 1. An unusual mixed osteolytic-osteoblastic metastatic pattern located at the lumbar vertebrae.

Table 3. Imaging features of the metastatic skeletal lesions (x-ray, CT)

Imaging features	Percentage of lesions (%)
Osteolytic	92.5
Cortical erosion & destruction	36.6
Soft tissue involvement	10.5
Mixed osteolytic-osteoblastic pattern (Fig.1)	8.2
Completely osteoblastic	2.3

Table 4. Palliation depending on total dose and fraction size

Total dose (cGy)	No palliated lesions / No lesions treated	(%)
< 3000	13/16	81.25
3000-4000	30/37	81.08
> 4000	9/13	69.23
Dose per fraction (cGy)	No palliated lesions / No lesions treated	(%)
< 200	2/3	67.00
201-300	21/26	80.76
301-400	8/9	88.88
401-500	10/15	66.66
> 500	11/13	84.61

that 91.1% of the lesions had a medullary origin. Scintigraphy uniformly depicted metastatic lesions as sites of increased uptake of Tc-99m. Magnetic resonance imaging was more specific in depicting the soft-tissue involvement.

Whenever imaging follow-up was performed to evaluate the response to treatment, certain radiological response patterns were identified. Recalcification, sclerotic rim and periostal reaction were the most common findings.

The 66 bone lesions -found in the 26 symptomatic patients - were treated with irradiation, and showed an effective palliative response rate of 79% (52/66). Table 4 demonstrates that the palliation of bone metastases was not related to total dose or fraction size.

In 18 (of the 26) symptomatic patients, 31 symptomatic bone lesions were treated with radiotherapy and concurrent chemotherapy and/or biphosphonates, while 15 asymptomatic lesions were treated only with chemotherapy and/or biphosphonates. Systemic chemotherapy was also given to the two asymptomatic patients with the metastatic lesions at the lumbar vertebrae. In all 20 patients, the disease progressed in extraskeletal sites. As shown in imaging follow-up, 61% of the symptomatic lesions responded to therapy; all of them were clinically palliated. All asymptomatic lesions treated with chemotherapy and/or biphosphonates did not respond radiologically or clinically, but progressed.

Median response duration to treatment was estimated to 2.6 months and median overall survival was estimated to 4.7 months.

Discussion

In our study, only 9.5% of the stage IV melanoma patients had skeletal involvement. A similar low percentage of antemortem diagnosis of bone metastases from malignant melanoma is reported in the literature.[1-4] Since clinical diagnosis of skeletal involvement is infrequent, little has been published describing the pattern and natural history of melanoma metastatic to the bone.

The limitation of our study is that we did not perform routine screening, so we do not know the exact incidence of skeletal metastases. Based on melanoma surveillance guidelines,[6,7] our patients were not routinely submitted to bone radionuclide scintigraphy. Nevertheless, we evaluated our patients during the follow-up with chest and abdominal computed tomography, so we were able to detect the majority of skeletal metastases. Melanoma bone metastases occur more frequently in the axial skeleton, and are therefore easily diagnosed by computed tomography.[8,9] Nevertheless, the real incidence of

osseous disease might be slightly higher than 9.5%, since appendicular bone metastases could not be depicted by thoracic and abdominal computed tomography.

Only 3.7% of our patients had bone metastases as the first and only site of recurrence; the rest of the patients had widespread disease in multiple metastatic sites. This is also in agreement with the literature.[5]

In our series, skeletal metastases were more frequent in patients with primary melanomas of the trunk and the head and neck area.

We also found that all patients with bone metastases had a thick or intermediate primary melanoma ($p<0.001$). Additionally, most patients had stage III disease prior to the development of skeletal metastases. Our findings may suggest that the patients with more advanced primary lesions are more likely to develop bone metastases, and should be more closely monitored.

Only 7.4% of our patients were asymptomatic and the skeletal involvement was found during routine imaging follow-up. The metastatic disease was located at the lumbar vertebrae and was detected by an abdominal computed tomography. In our series, axial metastases (86%) were more common than appendicular bone metastases and 54% of them were located in the spine. Our findings are similar to those previously reported, and suggest that whenever a computed tomography is performed to evaluate metastatic melanoma, the axial skeleton should be carefully examined.[8,9]

Bone radionuclide scintigraphy was nonspecific; all metastatic lesions were depicted as sites of increased uptake of Tc-99m. Plain radiographs and computed tomography images were diagnostic. In the literature, there are few reports of the imaging findings of skeletal melanoma metastases.[9-11] In our series, melanoma bone metastases were osteolytic with medullary origin. Lesion growth caused cortical erosion and destruction, pathologic fractures and soft-tissue involvement. Atypical skeletal metastases exhibited a mixed osteolytic-osteoblastic pattern or, even more infrequently, a completely osteoblastic pattern. Magnetic resonance imaging better depicted the extent of soft-tissue involvement.

The response assessment of bone metastases to therapy is difficult; in most cases, decisions about the efficacy of treatment are based on symptomatic response or change in extraskeletal metastatic disease. In our study, radiographs and computed tomography were useful in evaluating the tumor's response to treatment.

One could argue that since the real incidence of bone metastases in clinical series is low, the role of computed tomography or other imaging studies is only complementary. Nevertheless, we showed that serial radiographs or computed tomography are essential in establishing the diagnosis, guiding the treatment planning and assessing the tumor's response to treatment.

In our series, radiotherapy offered an effective palliation rate of 79%. We believe that it still represents the treatment of choice in this subgroup of patients; the treatment with chemotherapy and/or biphosphonates did not appear as effective. We agree with Rate and al. that concurrent chemotherapy has no influence on palliation.[12] We found that in palliative treatment of bone lesions from melanoma, the application of high total dose or high fraction size was not advantageous at all. High doses should be avoided since they do not offer more effective palliation and can create greater complications. Similar results were reported by Konefal *et al.*[13] in the analysis of dose fractionation in the palliation of bone and brain metastases from malignant melanoma.

Despite the palliation offered with radiotherapy, our patients' prognosis was poor. Median survival was similar to the one previously reported in the literature[1,2,5] and esti-

mated to 4.7 months. Even if patients with thick or intermediate primary cutaneous melanomas could be more closely monitored in order to detect asymptomatic bone metastases, no change in palliation or survival would be achieved.

In conclusion, we recommend a skeletal evaluation with radiographs or computed tomography - whenever symptoms develop - and a careful examination of the axial skeleton in the patients with advanced primary melanomas. The life expectancy of these patients is short, but conventional fractionation radiotherapy can offer effective palliation to most of these patients. It is therefore worthwhile to pursue the diagnosis.

References

1. Lee YT. Malignant melanoma: patterns of metastasis. *CA Cancer J Clin* 1980; **30:** 137-41.
2. Balch CM, Soong S-J, Murad TM. A multifactorial analysis of melanoma. IV. Prognostic factors in 200 melanoma patients with distant metastases (stage III). *J Clin Oncol* 1983; **1:** 126-9.
3. Budman DR, Camacho E, Wittes RE. The current causes of death in patients with malignant melanoma. *Eur J Cancer* 1978; **14:** 327-9.
4. Amer MH, Al-Sarraf M, Vaitkevicius VK. Clinical presentation, natural history and prognostic factors in advanced melanoma. *Surg Gynecol Obstet* 1979; **149:** 687-90.
5. Balch CM, Soong S-J, Shaw HM, Urist MM, Mc Carthy WH. An analysis of prognostic factors in 8500 patients with cutaneous melanoma. In: Balch CM, Houghton AN, Milton GW, Sober A, Soong S-J, editors. *Cutaneous melanoma*. Philadelphia: J-B Lippincot; 1992. p. 165-71.
6. Huang CL, Provost N, Marghoob AA, Kopf AW, Levin L, Bart RS. Laboratory tests and imaging studies in patients with cutaneous malignant melanoma. *J Am Acad Dermatol* 1998; **39:** 451-63.
7. Gershenwald JE, Buzaid AC, Ross MI. Classification and staging of melanoma. *Hematol/ Oncol Clin N Am* 1998; **12:** 737-65.
8. Pattern RM, Shuman WP, Teefey S. Metastases from malignant melanoma to the axial skeleton: a CT study of frequency and appearance. *AJR* 1990; **155:** 109-12.
9. Potepan P, Spagnoli I, Danesini GM, Laffranchi A, Gadda D, Mascheroni L, et al. The radiodiagnosis of bone metastases from melanoma. *Radiol Med* (Torino) 1994; **87:** 741-6.
10. Stewart WR, Gelberman RH, Harrelson JM, Seigler HF. Skeletal metastases of melanoma. *J Bone Joint Surg Am* 1978; **60:** 645-9.
11. Fon GT, Wong WS, Gold RH, Kaiser LR. Skeletal metastases of melanoma: radiographic, scintigraphic, and clinical revue. *AJR* 1981; **137:** 103-8.
12. Rate WR, Solin LJ, Turrisi AT. Palliative radiotherapy for metastatic malignant melanoma: brain metastases, bone metastases, and spinal cord compression. *Int J Radiat Oncol Biol Phys* 1988; **15:** 859-64.
13. Konefal JB, Emami B, Pilepich MV. Analysis of dose fractionation in the palliation of metastases from malignant melanoma. *Cancer* 1988; **61:** 243-6.