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ORIGINAL STUDY

Surgical treatment of skeletal metastases in 31 melanoma patients

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The authors retrospectively studied 31 patients with malignant melanoma who were surgically treated for 34 skeletal metastases between 1987 and 2007. The aim was to evaluate the role of orthopaedic surgery and to identify factors related to survival. The patients were operated on for spinal cord compression (n = 12) and metastatic destruction in a long bone (n = 17), or other locations (n = 5). The median survival after surgery was 1.9 months (range : 0-40). The survival rate was 0.39 at 3 months, and 0.13 at 1 year. Four of 34 operations led to failure necessitating reoperation. A prolonged delay between diagnosis and surgery, radical excision, a solitary skeletal metastasis, radiotherapy, a perioperative lactate dehydrogenase (LDH) level ≤ 8 μkat/L (p = 0.04) and a preoperative haemoglobin level > 11.5 mg/dL (p = 0.003) had a favourable prognostic impact. A vertebral localization was unfavourable. These prognostic factors may help identify which melanoma patients with symptomatic skeletal metastases will benefit from orthopaedic surgery. This study represents the largest reported cohort surgically treated for skeletal metastasis of malignant melanoma at a single institution.

Keywords : melanoma ; skeletal metastases ; prognosis ; hemoglobin ; lactate dehydrogenase.

INTRODUCTION

Six out of 10 patients with disseminated malignant melanoma develop skeletal metastases during the course of their disease. The skeleton is the fifth most common site of metastatic disease following soft tissue/lymph nodes, lung, liver and brain *(9,13)*. Skeletal metastases seriously affect the quality of life of melanoma patients by causing pain, pathologic fracture, paraparesis, and hypercalcaemia. The goals of palliative orthopaedic surgery are restoration of function and alleviation of pain. The benefit of this treatment is difficult to predict since many patients surgically treated for pathologic fractures or paraparesis have a few months left to live, while others might live for years. The authors suspected that the prognosis was particularly poor compared to patients operated on for bone metastases from other primary tumours. Moreover, surgical treatment of bone metastases in melanoma patients was not common in their institution. The aim of the study was to identify factors related to survival and to evaluate the role and success rate of orthopaedic surgery in melanoma patients with symptomatic skeletal metastases.

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Table I. — Baseline data at diagnosis

Baseline characteristics at primary diagnosis		Number
Gender	Male	24
	Female	7
Type of melanoma*	Superficial spreading	15
	Nodular	10
	Unclassifiable	5
	Mucosal	1
	Unknown primary site	2
Primary tumour site*	Trunk	24
(29 cutaneous lesions in 27 patients)	Leg	4
	Arm	1
	Mucosal	1
	Unknown primary site	2
	Data unavailable	1
Breslow thickness**	≤ 1 mm	11
(29 cutaneous lesions in 27 patients)	1.01-2.0 mm	8
	2.01-4.0 mm	4
	> 4.0 mm	6
Ulceration**	Present	9
(29 cutaneous lesions in 27 patients)	Absent	20

* 2 patients had 2 primary melanomas
** Cutaneous melanomas only.

PATIENTS AND METHODS

This study was based on a consecutive series of 31 patients with malignant melanoma treated surgically for 34 metastatic lesions, from 1987 through 2007. Data were collected from the Regional Melanoma Registry at the Stockholm-Gotland Oncological Centre and from the Karolinska Skeletal Metastasis Register. The Skeletal Metastasis Register is a quality-control database which prospectively collects individual-based information about cancer patients surgically treated for spinal and non-spinal complete or impending fractures due to skeletal metastases. No patient was lost to follow-up and none was still alive.

There were 7 women and 24 men (Table I) with a median age of 59 years (range : 22-74) at the primary diagnosis of melanoma. The group was representative according to age at diagnosis and histological type (see below), but had a greater than expected proportion of males. The median age at the time of surgery for existing or impending pathological fracture was 63 years (range : 23-78). The median time interval from the date of diagnosis of melanoma until the date of surgery for fracture was 3 years (range : 0-16). Only 4 of 31 patients had a solitary skeletal metastasis (Table II), without known extra-skeletal metastases, at the time of orthopaedic surgery, including 2 patients previously treated with lymphadenectomy for regional lymph node metastases. The remaining 27 patients had generalized disease with extra-skeletal metastases.

Types of melanoma (Table I). The superficial spreading melanoma (SSM) (less aggressive) was the most common histological type of primary melanoma (n = 15), followed by nodular melanoma (NM) (n = 10) (the most aggressive form of melanoma, growing more rapidly in thickness than in diameter). Five melanomas were unclassifiable. The data about two melanomas were lost, and there was a single mucosal melanoma. Altogether there were 33 primary sites, given that two patients had two primary lesions.

Table II. — Patient characteristics at time of orthopaedic surgery

		Number
Site of skeletal metastasis for surgery	Vertebral	12
	Humerus, femur and tibia	17
	Ulna	1
	Foot	2
	Pelvis	2
Tumour burden	Solitary skeletal metastasis*	4
	Multiple metastases	27

* No extra-skeletal metastases.

Primary tumour site (Table I). Twenty-seven patients had primary cutaneous melanoma, and two of these had two separate melanomas, totalizing 29 primary cutaneous lesions ; two had metastases without known primary site, one patient had a mucosal primary melanoma of the maxillary sinus, and one patient was devoid of data as to his primary localization.

Breslow thickness (Table I). Eleven out of 29 cutaneous melanomas had a low tumour thickness (Breslow ≤ 1.0 mm, pT1), and thus a relatively better prognosis.

Ulceration, a negative variable (Table I). Nine out of 29 cutaneous lesions were ulcerated, and 8 of these were thick, which made their prognosis even worse.

Site of skeletal metastases operated on (Table II). Twelve patients were surgically treated for spinal cord compression due to vertebral metastases, 17 for metastatic lesion of a long bone, 2 for a foot metastasis, 2 for a pelvic metastasis, and one for a metastasis in the ulna. Seven of the 12 vertebral lesions were located in the lumbar spine and 5 in the thoracic spine. Among the 17 long bone fractures, 8 were located in the humerus, 6 in the femur, and 3 in the tibia. Six were strikingly located distal to elbow and knee, which indicates that melanoma belongs to a small group of malignancies with this rare peculiarity. Tumour burden : 4 patients had a solitary skeletal metastasis, while the remaining 27 had multiple metastases. Lesions in the proximal part of the long bones predominated (n = 10), followed by diaphyseal lesions (n = 6), and one distal lesion. A complete fracture was evident in 19 surgically treated lesions, whereas 15 operations were performed for impending fractures. A complete pathologic fracture was evident in 5 of 12 vertebral lesions : in all 8 lesions in the humerus, in 4 of 6 femoral lesions, in one of 3 lesions in the tibia, in the only ulna lesion and in none of the 2 foot and 2 pelvic lesions.

Surgical treatment

The metastatic lesions were treated in a variety of ways, based on their extent and anatomic locations. The 12 vertebral lesions were treated with laminectomy, followed in 5 cases by stabilization with pedicle screws and rods. All 8 humeral fractures were treated with an intramedullary nail, and all nails except one were interlocked. Of the 6 metastases in the femur, 2 were located in the femoral neck and were surgically treated with uncemented hemi-prostheses. One intertrochanteric fracture and one fracture in the distal femur were treated with glide-screw plates in combination with curettage and cement. Two diaphyseal lesions were treated with interlocked intramedullary nails. All 3 tibial lesions were located in the proximal part of the bone and were treated with curettage followed by cementation. In one of these cases, a plate was added to increase stability. One of the tibial lesions was initially misdiagnosed as a sarcoma and treated with curative intent. In this case, excision with wide margin was followed by reconstruction with a massive allograft. The 2 pelvic lesions both involved the acetabulum and were treated with an acetabular reinforcement ring in combination with total hip arthroplasty. The 2 foot lesions included one in the calcaneus, treated with curettage and cement, and one lesion in metatarsals III and IV which was treated by excision without reconstruction. The ulnar fracture was treated with excision without reconstruction in combination with an external orthosis.

Postoperative radiotherapy

Fourteen out of 31 patients (45%) received postoperative radiotherapy, including 2 patients who did not complete the treatment. Half of these (n = 7) were treated for vertebral lesions. Eight patients received 30 Gy in 6 fractions and 1 patient was scheduled for this regimen but did not complete the treatment. Two patients received a single fraction of 8 Gy, both for humeral lesions. Two patients received total doses of 20 Gy in 4 and 5 fractions respectively. One patient was scheduled for 30 Gy in 3 fractions but did not complete the treatment.

Statistics

Median values and ranges were used as descriptive statistics. Kaplan-Meier analysis was used to construct the cumulative survival with 95% confidence intervals (CI). A chi-square test was used to evaluate the role of preoperative lactate dehydrogenase and hemoglobin levels. A p-value < 0.05 was considered to be statistically significant.

RESULTS

Survival

The median survival after surgery was only 1.9 months (range : 0-40). There were no perioperative deaths. The Kaplan-Meier survival rate for the entire series of 31 patients was 0.39 at 3 months, 0.19 at 6 months, and 0.13 at 1 year after surgery (Fig. 1). The median survival was better in the group with a *longer interval between diagnosis of primary tumour and surgery for skeletal metastasis* (Table III). Three of the 4 patients with a *solitary skeletal metastasis without known extra-skeletal metastasis* had a survival of 5 months or more. The median survival of this small group (n = 4) was 18.5 months (Table IV). The patient with the longest survival (40 months) had a solitary skeletal metastatic lesion initially misdiagnosed as a sarcoma and therefore surgically treated with *radical excision*. This patient did not receive postoperative

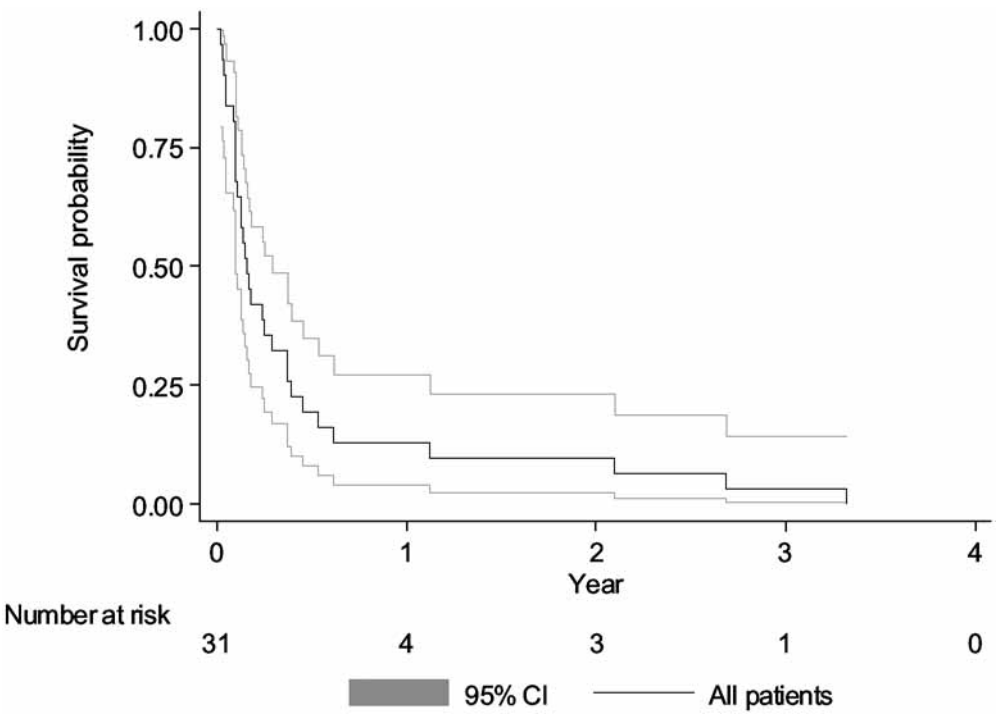

Fig. 1. — The Kaplan-Meier survival rate for the entire series of 31 patients after orthopaedic surgery for skeletal metastases

Table III. — Time from diagnosis until surgery

Time	Number	Median postoperative survival months (range)
0-3 years	18	1.5 (0-7)
≥ 4 years	12	2.5 (0-32)
Missing	1	

radiotherapy or adjuvant chemotherapy. The median survival was 3.1 months in the 14 patients receiving *postoperative radiotherapy* (Table IV) and 1.8 months in the 17 non treated patients. Fifteen patients received chemotherapy (Table IV), including one patient who was treated with alpha-interferon ; their median survival period was 4 months, well above the average of 1.9 months.

Impact of perioperative *lactate dehydrogenase (LD) level,* a measure of tissue necrosis (Table V). All patients with a survival of more than 6 months had a LD level of ≤ 8.0 μkat/L at the time of surgery. Patients with ≤ 8.0 μkat/L of LD had a better postoperative survival (median 3.5) than those with > 8.0 μkat/L (median 1.5) ($p = 0.042$). Patients with a *preoperative haemoglobin level* (Table VI) of ≤ 11.5 mg/dL had a worse postoperative survival than those with > 11.5 mg/dL ($p = 0.003$). Influence of *vertebral lesions*. The median survival after surgery for vertebral lesions was only 1.5 months, i.e. less than the overall median survival of 1.9 months. The 3 patients with a survival exceeding 2 years all had non-vertebral metastases (Table VII).

Complications and re-operations

There were no recorded systemic complications during the postoperative hospital care following any of the 34 surgical procedures. Four of 34 procedures (0.12) led to failures necessitating re-operation : 2 in patients with vertebral metastases and the other 2 in patients with metastases in the tibia. Thus, 2 of 12 patients surgically treated for paraparesis due to spinal cord compression were re-operated. One of these patients, initially treated with a laminectomy, was re-operated 2 months later with excision of a local recurrence of the tumour. The patient had not received postoperative radiotherapy. The second patient had been surgically treated with laminectomy and stabilization with pedicle screws and rods. He received postoperative radiotherapy with 30 Gy and later also systemic chemotherapy due to progression of disease. This patient was re-operated 13 months after initial surgery with renewed stabilization due to progressive kyphosis and severe pain caused by local recurrence of the

Table IV. — Postoperative survival and treatment

		Number	Median (range) months
All patients		31	1.9 (0-40)
Site of metastasis	Vertebral	12	1.5 (0-14)
	Solitary metastasis	4	18.5 (3-40)
Postoperative therapy	Radiotherapy	14	3.1 (1-32)
	Chemotherapy*	15	4.0 (1-32)

* including alpha-interferon therapy.

Table V. — Lactate dehydrogenase (LD) during perioperative period (± 3 months relative to date of surgery)

LD	Number	Median survival months (range)	p-value
≤ 8.0 μkat/L	14	3.5 (0-40)	p = 0.042*
> 8.0 μkat/L	10	1.5 (0-6)	
Missing	7		

* chi-square test.

Table VI. — Preoperative haemoglobin levels

Haemoglobin	Number	Median postoperative survival months (range)	p-value
< 11.5 mg/dL	10	1 (0-25)	p = 0.003*
≥ 11.5 mg/dL	15	4 (2-40)	
Missing	6		

* chi-square test.

Table VII. — Data of the 5 patients with the longest postoperative survival

Postoperative survival (months)	#1 40	#2 32	#3 25	#4 13	#5 7
Sex	Female	Male	Male	Male	Male
Age at surgery (years)	68	63	63	41	77
Breslow (mm)	0.3	1.2	2.6	0.7	1.4
Histological type	Missing	SSM	NM	SSM	Missing
Site of skeletal lesion Tumour burden	Tibia Single metastasis	Foot Single metastasis	Ulna Skeletal + soft tissue metastases	Vertebral Skeletal + visceral metastases	Vertebral Skeletal + soft tissue metastases
Time diagnosis to surgery (years)	0	12	16	3	3
Postoperative treatment	0	RT, CH	RT, CH	RT, CH	RT. CH
LDH-Ievel peri-operative Hemoglobin level (mg/L)	Normal 15.3	Normal 14.4	Normal 11.6	Normal 10.6	Normal 12.7

RT = radiotherapy, CH = chemotherapy, SSM = Superficial spreading melanoma, NM = Nodular melanoma.

tumour. One patient with a proximal tibial lesion, treated with curettage and cement, suffered a deep infection and was re-operated with removal of the cement and addition of antibiotic beads. One patient surgically treated with radical resection and reconstruction with a massive intercalary allograft in the diaphyseal tibia was re-operated one year later due to non-union of the graft. Bone graft from the iliac crest was added and led to an uneventful healing. There was one prosthetic dislocation among the 2 total hip replacements and none among the 2 hemi-prostheses.

DISCUSSION

Complications necessitating re-operation

The overall surgical failure rate of 0.12 (4/34) is comparable to previously reported re-operation rates in pathological fractures (*14,16*). The difficulties in surgical treatment of pathological fractures are by far greater than in traumatic fractures. Bone healing is often impaired because of extensive bone destruction, catabolic state and pre- or postoperative radiotherapy. Specific reasons for failure include improper implant selection, progression of bone destruction within the operative field, and poor initial fixation in osteoporotic bone. The absence of systemic complications in our study confirms previous findings that surgery is safe even in this group of seriously ill patients (*14*).

Survival

The prognosis is poor for stage IV melanoma (extension to distant lymph nodes and/or distant sites) with symptomatic skeletal metastases, which is illustrated in this study cohort with a median postoperative survival of only 1.9 months. The authors recently published a report on survival after

surgical treatment of skeletal metastases in lung cancer patients, and the median survival was 3 months (*15*). This indicates that melanoma patients have an even worse prognosis than lung cancer patients. Such short survival makes it more difficult to select patients for surgery, and one might argue that palliative orthopaedic surgery is not justified in a large proportion of patients with skeletal metastases of melanoma. However, the wide ranges of survival in this study with 1 patient out of 10 alive 1 year after surgery indicates that palliative surgery may be beneficial but only after very careful patient selection.

Factors which influence the decision making process include expected survival, overall medical condition, rehabilitation potential, and type of operation required. Patients with a very short life expectancy do not benefit from surgery because of rapid health deterioration and because of the difficulties in managing the postoperative rehabilitation in the terminal period.

Skeletal metastases of various origins : factors influencing survival

Several studies have identified clinical variables as being prognostically important in identifying patients with a very short life expectancy after an operation for skeletal metastases of various cancer types. Pathological fracture, visceral metastases, a haemoglobin level below 11.3 mg/dL, increasing number of bone metastases, and a primary diagnosis of lung cancer are examples of independent negative prognostic factors for 1-year survival after surgery (*3,5,8,10*). The current study is the first which specifically investigates the postoperative survival of melanoma patients surgically treated for skeletal metastases. The very short postoperative survival indicates that melanoma is an independent negative prognostic factor for 1-year survival, as is the case for lung cancer.

Skeletal metastases from melanoma : factors favourable for survival

A *longer time interval between initial diagnosis and surgery* was a favourable factor, probably because it reflected a good general health status. In general, survival was better among the 4 patients with a *solitary skeletal metastasis* (median 18.5 months). This has previously been reported for renal, breast, and lung cancer patients (*1,4,7,12*), but resection of such solitary metastases has not been shown to improve survival (*4*). In our study 3 of 4 patients with a solitary skeletal metastasis had a survival of 5 months or more. One of these patients had a *complete resection of a solitary metastasis* and lived for 40 months postoperatively. No conclusion can be drawn from this single case but a solitary skeletal metastasis in a melanoma patient without other manifestation of the disease might be an indication for a radical resection in hopes of achieving a long disease-free period.

The survival was better in the group of patients receiving *postoperative radiotherapy*, which probably reflects a general better health status. Indeed, radiotherapy is not considered in (pre)terminal patients.

Elevated levels of lactate dehydrogenase (LD), a measure of necrosis, are common in patients with generalized melanoma, and several studies have revealed a correlation with prognosis (*6*). Also the current study showed a significant difference ($p = 0.042$) in prognosis between the 14 patients with *LD levels* $\leq 8.0\ \mu kat/L$ and the 10 patients with *LDH levels* $> 8.0\ \mu kat/L$. A *normal haemoglobin level* might distinguish patients with a postoperative survival above 1.9 months.

Skeletal metastases from melanoma : factors unfavourable for survival

The median survival of patients with *vertebral metastases* was only 1.5 months, i.e. much less than the median survival of the group as a whole (1.9 months). Two of the 12 patients were re-operated. Does this short median survival justify spinal surgery ? The only prospectively randomized study known to the authors in this field (*11*) has shown that decompressive surgery in combination with spinal stabilization and radiation therapy is superior to treatment with radiation therapy alone in patients with spinal metastasis causing spinal cord compression. The authors feel that surgical treatment of the

tumour, with spinal stabilization when indicated, followed by radiation therapy, is justified in patients living at least 2-3 months if the patient can avoid becoming bedridden or losing the ability to ambulate independently. Additional radiation therapy for melanoma patients with paraparesis is indicated.

Skeletal metastases from melanoma : less important factors

There were no evident differences in survival after surgery in relation to *primary tumour thickness and histological type*, but the study group was small. Almost one third of the patients in this study had thin melanomas which constitutes a surprisingly high proportion (*2*).

REFERENCES

1. **Althausen P, Althausen A, Jennings LC, Mankin HJ.** Prognostic factors and surgical treatment of osseous metastases secondary to renal cell carcinoma. *Cancer* 1997 ; 80 : 1103-1109.
2. **Balch CM, Buzaid AC, Soong SJ *et al.*** Final version of the American Joint Committee on Cancer staging system for cutaneous melanoma. *J Clin Oncol* 2001 ; 19 : 3635-3648.
3. **Bauer HC, Wedin R.** Survival after surgery for spinal and extremity metastases. Prognostication in 241 patients. *Acta Orthop Scand* 1995 ; 66 : 143-146.
4. **Fuchs B, Trousdale RT, Rock MG.** Solitary bony metastasis from renal cell carcinoma : significance of surgical treatment. *Clin Orthop Relat Res* 2005 ; 431 : 187-192.
5. **Hansen BH, Keller J, Laitinen M *et al.*** The Scandinavian Sarcoma Group Skeletal Metastasis Register. Survival after surgery for bone metastases in the pelvis and extremities. *Acta Orthop Scand* Suppl 2004 ; 75 : 11-15.
6. **Jemal A, Siegel R, Ward E *et al.*** Cancer statistics, 2009. *CA Cancer J Clin* 2009 ; 59 : 225-249.
7. **Koizumi M, Yoshimoto M, Kasumi F, Ogata E.** Comparison between solitary and multiple skeletal metastatic lesions of breast cancer patients. *Ann Oncol* 2003 ; 14 : 1234-1240.
8. **Leithner A, Radl R, Gruber G *et al.*** Predictive value of seven preoperative prognostic scoring systems for spinal metastases. *Eur Spine J* 2008 ; 17 : 1488-1495.
9. **Manoso MW, Healey JH.** Metastatic cancer to the bone. In : DeVita VT Jr, Hellman S, Rosenberg SA, eds. *Cancer. Principles and Practice of Oncology*. 7th ed, Lippincott Williams and Wilkins, Philadelphia, 2005, pp 2368-2380.
10. **Nathan SS, Healey JH, Mellano D *et al.*** Survival in patients operated on for pathologic fracture : implications for end-of-life orthopedic care. *J Clin Oncol* 2005 ; 23 : 6072-6082.
11. **Patchell RA, Tibbs PA, Regine WF *et al.*** Direct decompressive surgical resection in the treatment of spinal cord compression caused by metastatic cancer : a randomised trial. *Lancet* 2005 ; 366 : 643-681.
12. **Sugiura H, Yamada K, Sugiura T, Hida T, Mitsudomi T**. Predictors of survival in patients with bone metastasis of lung cancer. *Clin Orthop Relat Res* 2008 ; 466 : 729-736.
13. **Tofe AJ, Francis MD, Harvey WJ.** Correlation of neoplasms with incidence and localization of skeletal metastases : An analysis of 1,355 diphosphonate bone scans. *J Nucl Med* 1975 ; 16 : 986-989.
14. **Wedin R, Bauer HC, Wersäll P.** Failures after operation for skeletal metastatic lesions of long bones. *Clin Orthop Relat Res* 1999 ; 358 : 128-139.
15. **Weiss RJ, Wedin R.** Surgery for skeletal metastases in lung cancer. *Acta Orthop* 2011 ; 82 : 96-101.
16. **Yazawa Y, Frassica FJ, Chao EY *et al.*** Metastatic bone disease. A study of the surgical treatment of 166 pathologic humeral and femoral fractures. *Clin Orthop Relat Res* 1990 ; 251 : 213-219.