Bone metastases in osteosarcoma patients treated with neoadjuvant or adjuvant chemotherapy

The Rizzoli experience in 52 patients

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Introduction **There have been no large-scale studies reporting the outcome of patients with osteosarcoma who first relapse with bone metastases, but there have been several case reports describing a much poorer prognosis for these patients than for those who relapse with lung metastases.**

Methods **We compared 52 patients with skeletal metastases as first relapse after neoadjuvant or adjuvant treatment for osteosarcoma of the extremity given at our institution between 1972 and 1999 with 371 contemporary patients treated with the same chemotherapy protocols, who first relapsed with lung metastases.**

Results **We found that the 52 patients with bone metastases had a higher rate of local recurrences (36% vs. 6%), a lower rate of remission (35% vs. 77%), and lower rates of 5-year event-free survival (11% vs. 27%) and overall survival (13% vs. 31%) ($p < 0.01$ for all comparisons).**

Interpretation **The prognosis of patients who relapse with bone metastases—unless they have a single late-appearing metastasis—is worse than the prognosis of patients who first relapse with lung metastases. There was no difference in outcome between patients with single, resectable and late-appearing skeletal metastases and patients relapsing in the lung.**

The first site of metastases in osteosarcoma patients is usually the lung. Skeletal metastases appearing as first relapse are uncommon and occur in about 10% of cases (Jeffree et al. 1975, Giuliano et al. 1984, Goorin et al. 1991, Bacci et al. 2001a) defined as methachronous osteosarcoma (Mirra 1989). After pulmonary relapse, a complete surgical resection of all overt metastases—sometimes combined with chemotherapy—offers long-term survival in about 25–30% of patients (Goorin et al. 1984, Beattie et al. 1991, Carter et al. 1991, Snyder et al. 1991 Saeter et al. 1995, Bacci et al. 1997). There have been no large-scale studies reporting the outcome of patients who first relapse with bone metastases, but several case reports describe a much poorer prognosis for patients who relapse with skeletal metastases (Fitzgerald et al. 1973, Simodynes et al. 1981, Giuliano et al. 1984, Howat et al. 1986, Huth and Eilber 1989, Wuisman and Enneking 1990, Marcove et al. 1994, Kalbermatten et al. 2000, Ferrari et al. 2003). On the other hand, two relatively recent papers (Aung et al. 2003, Jaffe et al. 2003) reported that the prognosis for methacronous osteosarcoma was similar to that after pulmonary relapse.

We examined clinicopathological features, treatment and outcome of 52 patients who relapsed with bone metastases among 1,148 patients who were treated with neoadjuvant (905) and adjuvant (243) chemotherapy for an osteosarcoma of the extremities at our institute between 1972 and 1999. These patients were compared with the 371

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Table 1. Protocols for adjuvant and neoadjuvant chemotherapy at the authors' institution, from 1972 to 1999

Adjuvant chemotherapy			
IOR/AD-1	V/ ldM–A		
IOR/AD-2	A		
IOR/AD-3	V/mdM–A		
IOR/AD-4	V/mdM–A vs V/hdM–A		
Neoadjuvant chemotherapy			
	Preoperative treatment	Postoperative treatment	
		Good responders	Poor responders
IOR-OS/N-1	mdM (750 mg/m^2 vs. 7.5 g/m^2)–P(ia)	mdM or hdM–P vs M–P–A	A–BCD
IOR-OS/N-2	hdM (8 g/m^2)–P(ia)/A	hdM–P–A	hdM–P–A–I/E
IOR-OS/N-3	hdM (10 g/m^2)–P (ia/iv)–A	hdM–P–A	hdM–P–A–I/E
IOR-OS/N-4	hdM (12 g/m^2)–PA (ia/iv)–PA(ia/iv))	M–P/I–P/A 3 cycles	M–P/I–PA 4 cycles
IOR-OS/N-5	hdM (12 g/m^2)–P(iv)–A–hdI	M–P–A-hdI	
IOR-OS/N-6	Arm a: mdM (12 g/m^2)–P(iv)/A	A–mdM–P	A–mdM–P–I
	Arm b: mdM (12 g/m^2)–P(iv)–ldA–I/P(iv)-I/A	M–P/A–I/P–I/A	

V: Vincristine; M: Methotrexate; A:doxorubicin; P: cisplatin; I: Ifosfamide; B: Bleomycin; C:Ciclophosphamide; D: Dactinomycin; ld: low doses; md: moderate doses; hd: high doses; ia: intraarterial; iv: intravenous.

patients treated during the same period with the same chemotherapy protocols who relapsed with lung metastases instead.

Patients and methods

Between 1972 and 1999, 1,148 patients aged less than 40 with primary high-grade osteosarcoma of the extremity were treated with adjuvant or neoadjuvant chemotherapy at our institute. The diagnosis was based on histological slides of tumor tissue obtained from biopsy and from the resected specimen. The tumor was classified as osteoblastic, fibroblastic, and chondroblastic conventional osteosarcoma, and telangiectatic and small cell osteosarcoma. This distinction was not possible in 112 cases of conventional osteosarcoma because of the coexistence of more than one of the features described, in similar proportions. Bone metastases were investigated with total body scan and by radiological examination, and they were confirmed by biopsy. Lung tomography was used to exclude lung metastases in patients treated before 1981, and CT scan was used from 1981 onward.

During the study period, 10 chemotherapy protocols were used (4 adjuvant protocols between 1972 and 1982, and 6 neoadjuvant protocols between 1983 and 1999). Chemotherapy included various combinations of methotrexate, doxorubicin, ifosfamide and cisplatin (Table 1). Some patients also received bleomycin, cyclophosphamide, dactinomiycin and vincristine. Details of the protocols have been reported previously (Campanacci et al. 1981, Bacci et al. 1986, 1990, 2000, 2001b, 2003, Ferrari et al. 1999). Surgery was amputation in 287 patients, limb salvage in 817 and rotationplasty in 38. 5 patients treated with neoadjuvant chemotherapy died of toxicity during the preoperative treatment while another patient was treated locally with radiotherapy since he developed unresectable lung metastases before scheduled time for surgery. Up until June 2004, among the 1,148 treated patients, 447 relapsed: 396 (89%) with metastases, 4 (1%) with local recurrence only, and 47 (11%) with metastases and local recurrence. The first site of metastasis was the lung in 371 patients (84%), bone in 52 (12%), lung and bone in 13 (3%), and other sites in 7 (2%).

This study includes the 52 patients (35 males) who had their first relapse in the skeleton and the 371 patients who had their first metastasis in the lung. 18 other patients had bone metastasis as second (or later) relapse and they were not included in the comparisons. Treatment of first and subsequent relapses consisted of chemotherapy or radiotherapy alone, or surgery and/or additional individualized chemotherapy. The mean follow-up time after relapse was 12 (1–26) years.

For both groups, the following parameters were evaluated: serum level of alkaline phosphatase at presentation and at first relapse, histological sub-

Table 2. Comparison of characteristics, treatment and outcome of patients with bone vs. lung metastases at first relapse

	Bone metastases	Lung metastases	P-value
Number of patients	52	371	
Median age (years)	15 (5–31)	17 (3–40)	0.05
High level of AP at presentation	50%	44%	0.5
High level of AP at relapse	42%	26%	0.02
Osteoblastic subtype	67%	47%	0.04
Volume > 150 mL	45%	37%	0.9
Primary tumor treated by amputation	13%	37%	0.001
Neoadjuvant chemotherapy	81%	66%	0.05
Local recurrence of primary tumor	36%	7%	< 0.001
Time to first relapse (months)	26	21	0.07
Single metastasis at first relapse	61%	24%	< 0.001
Unresectable metastases	62%	28%	< 0.001
Patient free of disease after relapse	35%	77%	< 0.001
5-year event-free survival after relapse	11%	27%	0.01
5-year overall survival	13%	31%	0.009

type, tumor volume at presentation, rates of amputation and rates of local recurrence, time to first relapse, number of metastases at first relapse, rates of unresectable metastases, 5-year event-free survival and overall survival at 5 years.

Statistics

The time for developing first methacronous skeletal osteosarcoma or first lung metastases was the time interval between the beginning of treatment of primary osteosarcoma to the diagnosis of bone or lung relapse.

Post-relapse survival was calculated from the time of first relapse until death or last follow-up. Event-free survival (EFS) and overall survival (OS) were calculated according to the Kaplan-Meier method. The effect of prognostic factors or differences between the two groups being compared, i.e. first relapse in bone vs. first relapse in lung, was assessed by the log-rank test.

Results

In the 52 patients who first relapsed with bone metastases, the site of the primary tumor was the femur in 37 patients, the tibia in 8, the humerus in 6, and other sites in 1. The primary tumors were classified as osteoblastic (33), small cell osteosarcoma (2), telangiectatic (2), fibroblastic (1), chondroblastic (1), and "undetermined" (13). None of the patients who relapsed with metahacronous osteosarcoma had a family history of sarcoma or malignancy. The median time to relapse was 26 (2–209) months and pain was the commonest symptom. In 2 patients with vertebral methacronous tumor, the pain was soon followed by paraplegia. 2 patients had asymptomatic bone metastases, found by scintigraphy (Table 2).

Number, site and treatment of bone metastases

32 patients relapsed with a single bone metastasis, 8 with 2 metastases, 9 with 3, and 3 with 4 metastases. The site of skeletal metastases was the pelvis in 21 patients, the spine in 21, the ribs in 9, the tibia in 5, the humerus in 5, and the skull in 2. 20 patients also developed local recurrence: 10 before the bone metastases, 6 after, and 4 simultaneously. Local treatment of bone metastases was surgery in 18 cases (resection in 14 and amputation in 4), radiotherapy in 23, chemotherapy alone in 1, and no treatment—or palliative treatment—in 10 cases. Surgery was performed in 16 cases with metastases located in the extremities and in 2 cases with metastases in the ribs. 16 patients treated with surgery and 11 treated with radiotherapy also received second-line chemotherapy. Of these 27, 13 patients had infusion of a high dose of ifosfamide (15 g/m2 for a 5-day continuous infusion), and the other 14 unoperated patients had some form of chemotherapy at other institutions.

Remission and survival

18 of the 52 patients (all with bone metastases in the extremities) became disease-free, whereas 34 did not. The rate of freedom from disease was significantly higher in the 18 patients with metastases located in the extremities, or the extremities and ribs, than in the 34 patients with metastases in the pelvis and/or spine: 28% (95%CI: 0–40) vs. 0% ($p = 0.004$). A disease-free status was reached by 5 of the 32 patients with 1 lesion and by none of

the 20 patients with more than 1 metastasis. The rate of freedom from disease was 29% (CI: 10–45) in patients with early relapse (< 25 months) and 44% (CI: 34–58) in patients with late relapse (p = 0.2). Of the 18 disease-free patients, 5 are alive and free of disease 8 (3–12) years after relapse. The other 34 patients developed new metastases located in the spine (2), in bone and lung (7), or only in the lung (25), and they were treated for the second relapse at other centers. At the time of writing, 2 are alive with disease and 32 have died of the tumor. Overall, the 5-year post-relapse event-free survival was 11% (95% CI: 0–21). The 5-year overall survival result was higher in patients with 1 metastasis than in patients with more metastases: 20% (95% CI: 9–30) vs. 10% (95%CI: 1–18). It was also higher in patients with metastases located in the extremities than in patients who did not have metastases located in the extremities, 33% vs. 9%, and in those with late relapse rather than early relapse: 33%, (95%CI: 15–52) vs. 9% (95%CI: 0–22), respectively.

Comparison with patients who relapsed with lung metastases (Table 2)

There were no differences in terms of sex and age, site and volume of the primary tumor, presence of pathologic fracture and serum levels of alkaline phosphatase at the time of the first diagnosis between the 52 patients who first relapsed with skeletal metastases and the 371 patients who first relapsed with lung metastases. Amputated patients had a lower rate of bone relapses compared to lung metastases, 13%, 95%CI: 1–26) vs. 37% (95%CI: 18–57) (p < 0.001), than had patients treated with neoadjuvant chemotherapy and conservative surgery. Accordingly, considering the type of relapse, most patients with skeleton metastases had been treated with limb salvage and neoadjuvant chemotherapy instead of amputation: 81% (95%CI: 62–94) vs. 66% (95%CI: 48–74) (p = 0.05). Patients who showed first relapse in bone also showed higher serum alkaline phosphatase at the time of relapse, 42% (95%CI: 39–57) vs. 26% (95%CI: 13–42) (p = 0.02), than those who relapsed in the lung. Interestingly, patients who relapsed in bone more often had local recurrence than patients who first relapsed in the lung: 36% (95%CI: 18–57) vs. 6% (95%CI: 0–22) (p < 0.001). As shown in Table 2, other significant differences unfavorable for patients who first relapsed with bone metastases in comparison with patients who first relapsed with lung metastases were the higher rate of cases with unresectable secondary lesions, the lower rate of patients who entered in remission after metastases treatment, the 5 year postrelapse event-free survival and the 5-year post relapse overal survival.

Discussion

If skeletal lesions are detected in a patient simultaneously with the discovery a primary osteosarcoma, this is termed "multifocal osteosarcoma" whereas bone metastases appearing later, after successful treatment of the primary tumor, are called metachronous tumors (Mirra 1989). Whether these skeletal lesions represent "real" metachronous tumors or metastases is unknown.

Two recent papers reported the outcome in patients with non-metastatic osteosarcoma, treated with surgery and chemotherapy, who first relapsed with bone metastases. Aung et al. (2003) reported results in 23 patients with non-metastatic, high-grade primary osteosarcoma who were treated at Memorial Sloan-Kettering Cancer Center between 1973 and 2000 and who had developed metachronous skeletal OS. Initial therapy included combination chemotherapy and surgery. Treatment of subsequent relapses consisted of chemotherapy or radiation alone, or surgery with or without additional individualized chemotherapy. The 5-year postmetachronous overall survival was 33% (95% CI: 13–53). At last follow-up (0.1–13 years), 5 patients were alive with no evidence of disease, 2 were alive with disease, and 16 patients had died. According to the disease-free interval between diagnosis of the primary tumor and diagnosis of bone metastases, patients with an interval longer than 2 years had a 5-year disease-free survival of 61%, while those who developed metachronous OS after less than 2 years had a 5-year disease-free survival rate of 8%.

Jaffe et al. (2003) described 11 cases of metachronous tumor, treated with single-agent cisplatin or ifosfamide. 6 patients died. 5 patients had survived 20–50 months after the appearance, treatment, and resection of the metachronous tumors.

3 patients had had a prior history of bilateral retinoblastoma and another patient displayed a Li-fraumeni syndrome. On the basis of this, Jaffe et al. postulated that methachronous osteosarcomas are secondary malignancies in which an inherent genetic factor causes the primary osteosarcoma, and later generates tumors in other bones. This process should become more evident with increased patient survival. However, such an association was not confirmed, either in our series or in the Sloan Kettering one (Aung et al. 2003).

Our findings, which involve a much higher number of patients, are worse than the ones reported in the two previously cited studies. As with the study of Aung et al. (2003), there was a small subset of patients who developed late, single and resectable bone metastases, and who achieved a long-term post-metachronous survival.

Another interesting difference we found between patients with bone metastases and those with lung metastases was the rate of local recurrence, which was higher in patients with bone metastases (36% vs. 7%; $p < 0.001$). This may indicate a different biology of the tumor.

In conclusion, our results indicate that, even if treated with aggressive surgery and chemotherapy, only 10% of patients with osteosarcoma of the extremity who relapse with bone metastases actually survive. 5 of 17 patients who relapsed with only 1 and a resectable metastasis survived, but only 1 of 35 of the remaining patients. The benefit of surgery for solitary bone metastases from other tumors, e.g. renal cell carcinoma, has been described previously (San Julian et al. 2003) and this appears to be true also for patients with osteosarcoma.

Contributions of authors

GB wrote most of the paper. GB, PP and AL were responsible for chemotherapy and follow-up data. FB made all histological examinations. EP made the statistical analyses. MV is responsible for data management and review of medical records. AB operated most of the patients and recorded surgical data.

No competing interests declared.

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