Nonmetastatic osteosarcoma of the extremity with pathologic fracture at presentation

Local and systemic control by amputation or limb salvage after preoperative chemotherapy

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ABSTRACT To determine whether a pathologic fracture in osteosarcoma of long bones has prognostic importance, and limb salvage can be safely performed in such cases, we reviewed the surgical treatment and oncologic results in 46 patients with nonmetastatic osteosarcoma of the extremity and pathologic fracture at presentation who had been treated in our Institution with neoadjuvant chemotherapy, between 1983 and 1999. Neoadjuvant chemotherapy was given according to 6 consecutive protocols. Surgery consisted of limb salvage (34 patients), amputation (11 patients) and rotationplasty (1 patient). The average follow-up was 11 (3–20) years. 28 patients remained continuously disease-free, 17 patients relapsed and 1 died of chemotherapy-related toxicity. Despite the high rate of limb salvage, only 2 local failures occurred, 1 after amputation and 1 after limb salvage. The 5-year disease-free survival and overall survival rateswere 59% and 65%, respectively, with no differences between amputated and resected patients. These results are similar to those obtained in 689 contemporary patients having an osteosarcoma without a pathologic fracture treated in our Institution, and using the same protocols for chemotherapy. We conclude that with neoadjuvant chemotherapy, osteosarcoma patients presenting with a pathologic fracture can be surgically treated like those with no fracture, and that limb salvage procedures do not increase the risk of local recurrence or death of these patients.

In osteosarcoma, the presence of a pathologic fracture at diagnosis (5–10% of all cases) has been historically associated with a poor outcome (Cooley and Pool 1940, McKenna et al 1966, O'Hara et al. 1968)). This may be because the fracture, causes a local hematoma, which facilitates dissemination of the tumor. For this reason, the presence of a pathologic fracture has been considered a contraindication for limb salvage, and an indication for an immediate amputation (Simon 1988, Finn and Simon 1991, Krugluger et al. 1993). However, only a few studies (Jaffe et al. 1987, Abudu et al. 1996, Scully et al. 1996, Natarajan et al. 2000, Scully et al. 2002) have specifically compared the local and systemic outcomes of limb salvage to amputation in osteosarcoma patients with a pathologic fracture.

To assess the features of patients presenting with a pathologic fracture and evaluate whether the presence of a pathologic fracture affected local and systemic control, we retrospectively analyzed 46 patients with a pathologic fracture who had been treated in the Rizzoli Institute.

Material and methods

Patient selection

46 of the 735 patients treated for an osteosarcoma of the extremity in our Institution between March

1983 and March 1999 presented with a pathologic fracture. The fracture was not displaced in 38 patients and was displaced in 8. All patients had stage IIB tumors. They were treated according to 6 neoadjuvant protocols for chemotherapy (Bacci et al. 1990, 1998, 2000, 2001a, 2001b) in which the criteria of eligibility were: (a) typical radiographic and histological features of primary, high-grade, central osteosarcoma; (b) tumor located in the extremities; (c) no history of cancer and no prior treatment elsewhere; (d) age under 40 years; (e) no associated disease contraindicating chemotherapy; (f) and no evidence of metastases at diagnosis.

Preoperative chemotherapy was given for 4–10 weeks, according to the protocol used. During this period the fractures were immobilized in plaster casts.

Surgery was scheduled 3 weeks after the preoperative chemotherapy. Before operation, the lesion was restaged. The type of surgery (amputation, limb salvage or rotationplasty) was chosen on the basis of size and location of the tumor, neurovascular involvement and skeletal maturity, and in resected patients, the type of reconstruction (prosthesis, bone graft, rod or plate and cement, vascularized fibula) was chosen according to the patient's lifestyle and preferences.

After surgery, the surgeons and pathologists reviewed the gross specimens to assess the surgical margins with Enneking's method (1987): radical, wide, marginal, or intralesional. The histologic analysis of tumor response was evaluated using Bacci et al.'s method (1990). The response to chemotherapy was classified as "poor" (less than 90% tumor necrosis) or "good" (90% or more tumor necrosis).

Postoperatively, chemotherapy was usually started within 7 days. After chemotherapy, patients were followed in the outpatient clinic every 2 months for 2 years, every 3 months in the 3rd year, and then every 6 months.

The clinical and radiological records of all the patients who entered the studies were retrospectively reviewed, and pertinent data were recorded.

Statistics

Various features between patients with or without a pathologic fracture at presentation were sought and compared using the chi-square test, and t-test, when appropriate. For each variable, the relative risk (RR) and respective 95% confidence interval (CI) of the pathologic fracture were calculated. The prognostic significance of a pathologic fracture was expressed as the probability of event-free survival (EFS) and overall survival (OS) in patients with pathologic fracture versus those without. Survival curves were calculated, using the Kaplan-Meier method and compared by means of the log-rank test.

Results

During the preoperative chemotherapy, no clinical or radiological progression of disease was documented. Surgery consisted of amputation in 11 cases, limb salvage in 34, and rotationplasty in 1. Amputation was performed in 5 of the 8 patients with displaced fracture and in 6 of the 38 with an undisplaced fracture. Reconstruction was achieved by prosthesis in 26 patients, by vascularized fibula combined with allograft in 1, by autograft in 2, and by allograft in 4. No reconstruction was necessary in 1 patient with a tumor in the fibula. Surgical margins were radical in 6 patients, wide in 34, marginal in 3 and intralesional in 3.

Histologic response to chemotherapy was good in 34 patients and poor in 12.

With a median follow-up of 11 (3–20) years, 28 patients remained continuously disease-free, 17 relapsed and 1 died of chemotherapy-related toxicity. The 5-year probabilities of DFS and OS were 59% and 65%, respectively. The average time to relapse was 24 (2–135) months, and the first signs of relapse were lung metastases in 15 cases and local recurrence in 2.

The DFS rate was not related to the patients' gender or age, tumor site, serum alkaline phosphatase levels at presentation, or fracture displacement. According to the histologic response to chemotherapy, the 5-year DFS was 70% for good responder patients and 33% for poor responders ($p = 0.04$). According to the surgical procedure, the 5-year DFS was 61% for the resected patients and 54% for amputated patients ($p = 0.7$)

The 2 local recurrences were diagnosed 20 and 22 months after starting treatment. The first patient had a tumor located in the proximal humerus,

surgery consisted of intralesional resection with prosthetic reconstruction and the histological response to chemotherapy was good. The local recurrence was treated with disarticulation, but shortly after the operation, the patient developed lung and bone metastases and died 7 months later. The second patient had a tumor in the proximal femur, treated with a marginal disarticulation. The histological response to chemotherapy was poor. Local recurrence was associated with lung metastases. The patient refused further treatment and died 5 months later. The first patient had been treated according to a protocol with MTX, CDP, and ADM, and the second patient had been treated according to a protocol with MTX, CDP, ADM and IFO.

The 15 patients who relapsed with lung metastases were all treated by metastasectomy, repeated twice in 4 cases, and 3 times in 2. 13 of these patients died with uncontrolled disease, mean 3 (1–11) years after starting the treatment. 10 patients had further chemotherapy. The remaining 2 patients are alive and free of disease 6 and 8 years after the last metastasectomy.

Surgical complications and functional results

Surgical complications were classified as "minor" if no surgical treatment was indicated, and "major" when they required surgery. Only 2 minor complications were seen in the 11 patients treated by amputation, while no complications were registered in the patient treated by rotationplasty. In the 34 patients treated by limb salvage, 31 complications (15 "minor" and 16 "major") occurred in 20. 12 patients had more than one complication. The major surgical complications were: graft fracture (2), prosthesis failure (2), internal fixation device failure (3), delayed union (2), wear of polyethylene bearings (5), infection (1) and wound slough (1). 9 patients had to undergo further surgery for major surgical complications: 2 underwent re-operation twice and one three times. The earliest major complication was observed 6 weeks and the last 5 years after surgery. The complications that required surgery were successfully managed without loss of the limb or, with the exception of 1 case, definitive removal of the reconstructive device.

Functional results were evaluated with Enneking et al.'s method (1990). They could not be assessed in 4 patients. In the 42 patients evaluated, 3 of the 9 amputated cases had good and 6 poor functional results. Of the 32 patients treated with limb salvage, the functional results were excellent in 2 cases, good in 20 and poor in 10. The patient treated with rotationplasty had a good functional result. The most unsatisfactory results were related to major complications (7) or to the lack of movement in patients treated with arthrodesis (3).

Comparison between patients with and without a pathologic fracture at presentation (Table 1)

The 2 groups were similar concerning age, gender, and the level of alkaline phosphatase in serum. A significant difference in distribution was found as regards: site, location in the affected bone, radiographic pattern, and histologic subtype of the tumor. Moreover, patients with a pathologic fracture at presentation had a higher mean tumor volume (408 mL) ($p = 0.0003$) than those without a pathologic fracture (214 mL). A high relative risk of pathologic fracture at presentation was found in patients with an osteosarcoma located in the humerus, or when the tumor involved the diaphysis, or in the case of a lytic appearance, and telangiectatic histologic subtype.

The percentage of amputated patients in the pathologic fracture group was significantly higher than in the group without a pathologic fracture (Table 2), which accounted for the higher incidence of radical surgical margins in the former group. The percentage of patients who underwent surgery with adequate surgical margins (radical + wide) was the same in patients with or without a pathologic fracture. We found no differences between the two groups as regards the histological response to chemotherapy and oncologic outcome. The 5-year disease-free survival was 59% in the pathologic fracture group versus 61% in the group of patients without a pathologic fracture and the local-control rate was the same in the two groups (Table 2). The mean relapse-free interval was 24 months in patients without a pathologic fracture and 22 months in those with a pathologic fracture. The 5-year overall survival was 65% in the pathologic fracture group and 67% in the other group.

Table 1. Features of patients presenting with pathologic fracture

Features	N	Pathologic fractures n (%)	P-value [a]	RR (95% CI)
Gender: Male	424	24 (6)	0.4	0.8 (0.64–0.96)
Female	311	22 (7)		1.3 (1.1–1.4)
Age: < 14 years	309	15 (5)	0.2	0.67 (0.5–0.85)
≥ 14 years	426	31 (7)		1.5 (1.3–1.7)
Site: Femur	392	22 (6)	0.0001	0.8 (0.63–0.95)
Tibia	203	5 (3)		0.31 (0.10–0.74)
Humerus	91	16 (17)		3.8 (3.6–3.9)
Other bones	48	3 (0.6)		0.99 (0.34–1.7)
Segment of bone involved				
Proximal	330	21 (0.6)	0.003	1.0 (0.87–1.2)
Diaphysis	40	8 (20)		3.7 (3.41–3.90)
Distal	365	17 (0.5)		0.59 (0.42–0.77)
Radiographic pattern				
Lytic	309	33 (1)	0.003	3.5 (3.3–3.7)
Mixed	93	5 (0.5)		0.84 (0.42–1.3)
Sclerotic	333	8 (0.2)		0.25 (0.03–0.54)
Histology				
Osteoblastic	473	20 (0.4)	0.03	0.43 (0.26–0.58)
Fibroblastic	61	6 (0.9)		1.7 (1.3–2.0)
Chondroblastic	74	3 (0.4)		0.62 (0.04–1.29)
Telangiectatic	58	9 (2)		2.8 (2.6–3.1)
Not classified	69	8 (1)		2.0 (1.8–2.3)
Serum alkaline phosphatase				
Normal	457	30 (0.6)	0.8	1.1 (0.96–1.3)
Elevated	278	16 (0.5)		0.87 (0.70–1.1)

[a] Chi-square test.

Table 2. Treatment and outcome in patients presenting with or without a pathologic fracture. Values are number (percentages)

	No pathologic fracture n = 689	Pathologic fracture n = 46	P-value
Surgery [a]			
Amputation	73 (11)	11 (24)	
Limb salvage	684 (84)	34 (74)	< 0.02
Rotationplasty	35 (5)	1 (2)	
Surgical margins [a]			
Radical	29 (4)	6 (15)	
Wide	593 (87)	34 (74)	
Marginal	50 (7)	3 (7)	0.4
Intralesional	12 (2)	3 (7)	
Tumor necrosis [a]			
> 90%	246 (36)	12 (26)	0.2
≥ 90%	438 (64)	34 (74)	
Local recurrence [a]	33 (5)	2 (4)	0.8
5-year DFS	(61)	(59)	0.3
5-year OS	(67)	(65)	0.4

[a] 5 patients died before surgery (4 of toxicity and 1 suicide)
DFS disease-free survival, OS overall survival

Discussion

The incidence of pathologic fractures in our series was 6%, which is similar to that reported by other authors (Jaffe et al. 1987, Abudu et al. 1996, Scully et al 1996, Natarajan et al. 2000). We found that a humeral or diaphyseal location, large tumor, a lytic radiographic pattern, or telangiectatic and fibroblastic subtype were risk factors for a pathologic fracture. Other authors have reported a higher risk of osteosarcoma of telangiectatic subtype (Huvos et al. 1982) or in the humerus (Abudu et al. 1996, Scully et al 2002).

The most important question about the management of a pathologic fracture in osteosarcoma is the surgical approach. 3 recent studies (Abudu et al. 1996, Scully et al 1996, 2002) evaluated patients with pathologic fractures treated by amputation or limb salvage. Abudu et al. (1996) reviewed the oncologic results in 40 patients with localized osteosarcoma treated by neoadjuvant chemotherapy and surgery in the same institution. 27 were treated with limb salvage and 13 were amputated. 5 patients had a local recurrence. All of them had been resected. In another monoinstitutional review (Scully et al. 1996), 10 patients were treated by limb salvage and 6 had an amputation. A local recurrence occurred in 3 patients who had been resected. In the last study (Scully et al. 2002), 8 institutions provided retrospective data on 52 patients with an osteosarcoma presenting with a pathologic fracture. 30 patients were resected and 22 amputated. A local recurrence occurred in 10 patients, but no difference was found between the resected and amputated case.

In our series, slightly more patients were treated with limb salvage (34/46) than in the studies mentioned above, but only 2 patients developed a local recurrence. This is less than in these 3 studies One explanation of our low local recurrence rate may be the type of neoadjuvant

chemotherapy. It is well known that in patients with osteosarcoma of the extremity treated with neoadjuvant chemotherapy, the treatment-induced necrosis, apart from its relation to outcome, is an independent prognostic factor of a local recurrence. In the 362 patients treated by the German Cooperative Osteosarcoma Study Group (COSS) (Bielack et al. 1996), using 3 different protocols for neoadjuvant chemotherapy, only 3% (5/202) of the patients with a good response to preoperative chemotherapy (< 10% viable tumor) relapsed locally, in contrast to the 9% (14/160) with a poor response patients (p = 0.01). Moreover, they had a high rate of local recurrence when limb salvage procedures were done in patients with a poor histological tumor response (8/50).

In the 540 patients with nonmetastatic osteosarcoma of the extremity, treated with neoadjuvant chemotherapy in our Institution between 1983 and 1994 (Bacci et al. 1998), the 7-year local recurrence rate was 5% in the 359 patients with tumor necrosis > 90 %, and 10% in the 181 patients with tumor necrosis < 90% (p = 0.001).

Recently, Eilber et al. (2001) reported that treatment-induced necrosis was an independent predictor not only of overall survival. but also of a local recurrence in patients who received neoadjuvant therapy for high-grade extremity soft tissue sarcomas: the 10-year local recurrence rate was 11% in patients with 95% or more tumor necrosis versus 23% in patients with tumor necrosis < 95% (p = 0.002).

On the basis of our results, we conclude that the presence of a pathologic fracture does not increase the risk of local recurrence in patients with osteosarcoma of the extremities. In patients with a pathologic fracture, the use of effective primary chemotherapy plays an important role in local control and it makes limb-sparing surgery possible in most patients.

No competing interests declared.

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