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Effect of Erroneous Surgical Procedures on Recurrence and Survival Rates for Patients with Osteosarcoma

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To determine whether inappropriate surgical procedures based on an initial misdiagnosis affected recurrence and survival rates, we retrospectively reviewed the surgical treatment and results of 117 patients with high-grade osteosarcomas treated from January 1, 1990 to December 31, 2000. Nine patients had intralesional curettage performed at other institutions based on an erroneous diagnosis of a benign lesion. Two of the nine patients had amputations and seven patients had limb-salvage procedures. Of the 108 patients who were not misdiagnosed, six patients had amputations and 102 patients had limb-salvage procedures. All patients received neoadjuvant therapy. Fifteen of the 117 patients had local recurrences. Patients who had erroneous surgical procedures based on the initial misdiagnosis of osteosarcoma had an increased risk of local recurrence and decreased 10-year survival rate. Response to adjuvant therapy and the amount of previous violation of natural tumor barriers should be evaluated carefully before deciding surgical treatment.

Level of Evidence: Level III, therapeutic study (Retrospective comparative study). See the Guidelines for Authors for a complete description of levels of evidence.

The current treatment for most high-grade osteosarcomas is multiagent chemotherapy followed by tumor resection with adequate margins. After different combinations of platinum, ifosfamide, doxorubicin, and high-dose methotrexate, limb salvage can be performed in more than 80% of patients with a 50% to 70% survival rate.[2,9,15]

Conditions for limb-salvage surgery should include preservation of the natural margins of tumors usually enhanced by chemotherapy. However, these margins might be disrupted before final surgery by an extensive open biopsy, a pathologic fracture, or by a previous invasive procedure because of an erroneous diagnosis. There is evidence that under certain circumstances, patients with an osteosarcoma who experience a pathologic fracture still may be treated with limb salvage without altering the prognosis.[1,3,13]

We asked whether an inappropriate surgical intervention attributable to an erroneous diagnosis in a group of patients with osteosarcoma affected recurrence and survival rates.

MATERIALS AND METHODS

We retrospectively reviewed 117 consecutive patients with high-grade osteosarcomas (according to Enneking staging[7]) surgically treated from January 1, 1990 to December 31, 2000. Nine patients (7%; 95% CI, 2–12%) had intralesional curettage performed elsewhere based on an erroneous initial biopsy. The primary histologic diagnoses included aneurysmal bone cyst (n = 5), osteomyelitis (n = 2), osteoblastoma (n = 1), and nonossifying fibroma (n = 1). Definite histologic diagnoses were conventional osteosarcoma (n = 7) and telangiectatic osteosarcoma (n = 2). The surgical treatment for these nine patients after multiagent therapy included two amputations and seven limb-salvage procedures (Table 1). In the 108 patients with no initial misdiagnosis, surgery after neoadjuvant therapy included six amputations and 102 limb-salvage procedures. Sixty-one of the 117 patients were males and 56 patients were females with a mean age of 19 years (range, 5–65 years). The primary lesions were located in the femur (n = 70), tibia (n = 28), pelvis (n = 6), fibula (n = 5), humerus (n = 4), radius (n = 2), talus (n = 1), and metatarsus (n = 1). We followed patients an average of 71 months (range, 2–176 months).

Staging studies included anteroposterior (AP) and lateral radiographs of the affected bone, magnetic resonance imaging (MRI) of the affected segment, computed tomography (CT) of

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Each author certifies that his or her institution has approved the reporting of this case report, that all investigations were conducted in conformity with ethical principles of research, and that informed consent was obtained.
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TABLE 1. Data for Patients with Initial Misdiagnoses

Patient Number	Age (years)	Gender	Erroneous Initial Diagnosis	Location	Enneking Stage	Limb Status	Necrosis (percent)	Local Recurrence	Followup (months)	Patient Status
1	35	Male	OB	Pelvis	III	Preserved	60	+	17	D
2	21	Male	OM	Proximal tibia	IIB	Preserved	97	–	42	D
3	5	Female	ABC	Proximal femur	III	Not Preserved	40	–	16	D
4	25	Male	NOF	Distal femur	IIB	Preserved	100	–	61	ANED
5	15	Male	OM	Distal femur	III	Preserved	98	+	96	D
6	21	Female	ABC	Talus	III	Preserved	40	+	70	ANED
7	16	Male	ABC	Distal femur	IIB	Not preserved	70	–	20	D
8	19	Male	ABC	Distal femur	IIB	Preserved	90	+	24	D
9	11	Female	ABC	Distal femur	IIB	Preserved	40	+	63	ANED

OB = osteoblastoma; OM = osteomyelitis; ABC = aneurysmal bone cyst; NOF = nonossifying fibroma; ANED = alive with no evidence of disease; D = deceased

the lungs, and a total body bone scan. Twelve of the 117 patients (10%; 95% confidence interval [CI], 5–15%) had pulmonary metastases at first consultation. These 12 patients had Enneking Stage III disease, and the remaining patients had Enneking Stage IIB disease.

All patients received neoadjuvant chemotherapy including ifosfamide, doxorubicin, and high-dose methotrexate or cisplatin. Histologic response to neoadjuvant chemotherapy was determined in 108 patients. A good response was considered when patients had greater than 90% tumor necrosis, and a poor response was considered when patients had less than 90% tumor necrosis.

Local tumor control was achieved by amputation in eight of the 117 patients (7%) and by limb-salvage procedures in 109 patients (93%).

The local recurrence rate and overall survival rates were estimated by the Kaplan-Meier method. Testing the difference between or among survival curves was done using the log-rank test. The statistical significance of the differences was evaluated with the criterion of $p < 0.05$.

RESULTS

The overall Kaplan-Meier 5-year survival rate was 64% (95% CI, 55–73%). Factors affecting survival curves were inappropriate intralesional curettage based on an erroneous diagnosis of a benign lesion, the histologic response to chemotherapy, the initial presence of lung metastases, and local recurrences.

Fifteen of the 117 patients had local recurrences (13%; 95% CI, 7–19%).

Patients with previous intralesional curettage had a greater ($p = 0.0026$) mean recurrence rate (55%; 95% CI: 23–88%) compared with patients whose initial treatment was without an initial erroneous diagnosis (9%; 95% CI, 3–13%). Five of seven patients treated with limb-salvage procedures in the group with previous curettage had local recurrences (Fig 1). The nine patients with inappropriate intralesional curettage also had lower ($p = 0.067$) mean 5-year and 10-year survivorship rates (44%, 95% CI, 12–56%; and 22%, 95% CI, 0–47%, respectively) compared with patients without initial misdiagnoses (66% 95% CI, 57–75%; and 64%, 95% CI, 55–73%, respectively) (Fig 2).

The histologic response to chemotherapy was good (> 90% tumor necrosis) in 57% (95% CI, 48–66%) of patients and poor (< 90% tumor necrosis) in 43% (95% CI, 34–52%). Disease-free survival rates were greater ($p = 0.001$) in patients with a good response (84%; 95% CI, 75–93%) than in patients with a poor response (45%; 95% CI: 31–59%).

The 5-year overall survival rate for patients with pulmonary metastases at first consultation (28%; 95% CI, 15–41%) was lower ($p = 0.004$) compared with the rate for patients without pulmonary metastases (70%; 95% CI, 61–79%).

The 5-year post-recurrence survival rate for patients with local recurrence (33%; 95% CI, 10–57%) was lower ($p = 0.001$) than the rate for patients without local recurrence (65%; 95% CI, 56–74%).

DISCUSSION

The prognosis for most musculoskeletal tumors depends on therapeutic techniques and their stage at diagnosis. Delayed diagnosis allows tumor progression and previously uncontaminated tumor margins may change the tumor stage, which substantially affects the necessary surgical technique and prognosis.

Our study has several limitations. This was a retrospective clinical study with potentially uncontrolled confounding variables, such as the small number of patients with erroneous surgical procedures in different anatomic sites. Additionally, the chemotherapeutic regimens and local tumor control were not standardized between groups. There were more Stage III osteosarcomas in the group with in-

Fig 1A–E. (A) Anteroposterior radiographs show the patient's knee (Patient 5) at the time of the erroneous diagnosis, and (B) after débridement. (C) Magnetic resonance imaging was done after the patient was diagnosed with an osteosarcoma. (D) An AP radiograph shows the patient's knee 3 years after resection of the distal femur and reconstruction with an intercalary allograft. (E) An axial CT scan was performed at the time of the biopsy of the local recurrence 5 years postoperatively. The scan shows the needle inside a soft tissue mass in the medial aspect of the thigh.

appropriate initial treatment than in the group initially treated at our institution. The variable exposure of normal tissues during the initial inappropriate invasive procedure and variations in individual responses to chemotherapy also may have influenced surgical treatment.

Surgeons sometimes perform erroneous intralesional procedures because benign aggressive tumors occur in patients in the same age group and the tumors can have similar radiographic appearance, clinical symptoms, or joint location. Histologically, osteosarcomas can appear as an aneurysmal bone cyst or as an osteoblastoma.[10,12] Five of the nine patients were misdiagnosed histologically as having an aneurysmal bone cyst and one patient was misdiagnosed as having an osteoblastoma (Fig 3). Initial misdiagnosis is not uncommon in patients referred to musculoskeletal tumor centers. The nine patients who were misdiagnosed represented 7% of the patients with osteosarcomas referred to our institution during the study period.

After the initial intralesional procedure, we established the final diagnosis of an osteosarcoma from the curetted tissues. The steps to obtain local control of the tumor under these circumstances might be controversial. A previous inappropriate intralesional procedure in a patient with an osteosarcoma is considered an indication for an amputation by some authors.[8,14] These surgeons consider

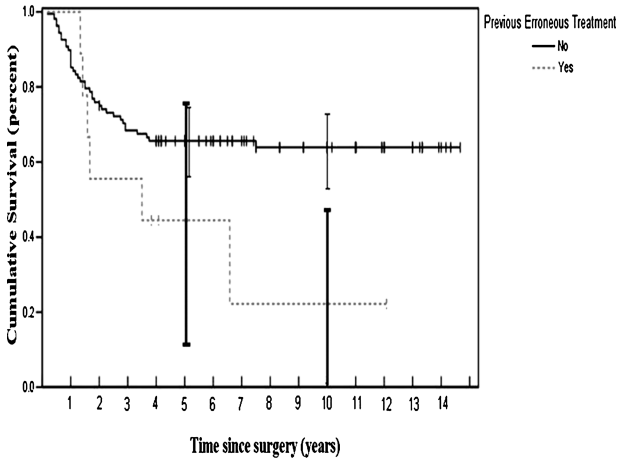

Fig 2. Kaplan-Meier survivorship curves compare patients who had an initial erroneous treatment based on a benign lesion with patients who did not have erroneous treatment. The bars indicate a 95% confidence interval.

radical treatment mandatory because of potential gross tumor contamination of surrounding tissues. However, we consider this situation similar to that after a pathologic fracture, where patients could receive neoadjuvant chemotherapy and have a limb-salvage procedure. This latter view is supported by others who suggest that patients with an osteosarcoma and pathologic fracture should be treated surgically according to their response to chemotherapy and fracture union after adjuvant therapy.[3,13] When patients responded well to chemotherapy, limb-salvage procedures did not increase the risk of local recurrence or death.[3,13] In some patients with minor intralesional curettage, the erroneous procedure may be comparable to an incisional biopsy, and therefore, we considered limb salvage based on the clinical response to chemotherapy (reduction of symptoms and improvement seen on radiographs and MRI scans). All of our patients received neoadjuvant chemotherapy, even those previously treated with an erroneous intralesional procedure.

The local recurrence and survival rates in the nine patients who were misdiagnosed and who were treated with inappropriate intralesional curettage resulted in an increased local recurrence rate and a lower life expectancy than patients initially treated at our institution with no misdiagnosis. Additional risk factors associated with poor prognosis included a poor response to chemotherapy (low percentage of tumor necrosis), initial lung metastases, and recurrent local disease.[4–6,11,16,17]

Fig 3A–G. (A) An AP radiograph of the knee shows an osteolytic lesion in the lateral condyle (Patient 4). (B) A coronal MR image of the knee shows the lesion. (C) The postoperative radiograph shows the knee after intralesional curettage and filling of the defect with cement that were done based on an erroneous diagnosis. (D) A coronal MR image performed after neoadjuvant chemotherapy shows no evidence of bone tumor invasion or soft tissue mass. (E) An AP radiograph was obtained after resection of the distal femur and reconstruction with an osteoarticular allograft. (F) An AP radiograph performed 1 year after reconstruction shows no evidence of local recurrence, but there is evidence of loosening and rupture of the distal screws. (G) An AP radiograph shows the knee 5 years after initial reconstruction. Healing of the osteotomy after autograft and replating can be seen, and the patient has no evidence of local recurrence.

Our findings suggest that limb-salvage procedures increased the local recurrence rate and decreased the survival rate in patients with osteosarcomas treated previously with erroneous surgical procedures based on an initial misdiagnosis. However, after more than 5 years followup, half of our patients with preserved limbs were free of disease. Future advances to establish surgical margins in this difficult group of patients may determine precise indications for limb salvage.

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