

Survival, Recurrence, and Function After Epiphyseal Preservation and Allograft Reconstruction in Osteosarcoma of the Knee

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Received: 3 July 2014 / Accepted: 20 October 2014 / Published online: 29 October 2014
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Abstract

Background Bone tumor resections for limb salvage have become the standard treatment. Recently, intercalary tumor resection with epiphyseal sparing has been used as an alternative in patients with osteosarcoma. The procedure maintains normal joint function and obviates some complications associated with osteoarticular allografts or endoprostheses; however, long-term studies analyzing oncologic outcomes are scarce, and to our knowledge, the concern that a higher local recurrence rate may be an issue has not been addressed.

Questions/purposes We wanted to assess (1) the overall survival in patients treated with this surgical technique; (2) the percentage of local recurrence and limb survival, specifically the incidence of recurrence in the remaining epiphysis; (3) the frequency of orthopaedic complications, and, (4) the functional outcomes in patients who have undergone intercalary tumor resection.

One of the authors certifies that he (LA-T), or a member of his or her immediate family, has or may receive payments or benefits, during the study period, an amount in excess of USD \$10,000 from a commercial entity (Stryker Americas, Miramar, FL, USA). All ICMJE Conflict of Interest Forms for authors and *Clinical Orthopaedics and Related Research* editors and board members are on file with the publication and can be viewed on request. Each author certifies that his or her institution approved or waived approval for the human protocol for this investigation and that all investigations were conducted in conformity with ethical principles of research.

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Methods We analyzed all 35 patients with osteosarcomas about the knee (distal femur and proximal tibia) treated at our center between 1991 and 2008 who had resection preserving the epiphysis and reconstruction with intercalary allografts. Minimum followup was 5 years, unless death occurred earlier (mean, 9 years; range, 1–16 years), and no patients were lost to followup. During the study period, our indications for this approach included patients without metastases, with clinical and imaging response to neoadjuvant chemotherapy, that a residual epiphysis of at least 1 cm thickness could be available after a surgical margin width in bone of 10 mm was planned, and 16% of patients (35 of 223) meeting these indications were treated using this approach. Using a chart review, we ascertained overall survival of patients, oncologic complications such as local recurrence and tumor progression, limb survival, and orthopaedic complications including infection, fracture, and nonunion. Survival rates were estimated using the Kaplan-Meier method. Patient function was evaluated using the Musculoskeletal Tumor Society (MSTS)-93 scoring system.

Results Overall survival rate of the patients was 86% (95% CI, 73%–99%) at 5 and 10 years. Five patients died of disease. No patient had a local recurrence in the remaining bony epiphysis, but three patients (9%; 95% CI, 0%–19%) had local recurrence in the soft tissue. The limb survival rate was 97% (95% CI, 89%–100%) at 5 and 10 years. Complications treated with additional surgical procedures were recorded for 19 patients (54%), including three local recurrences, two infections, 11 fractures, and three nonunions. In 10 of these 19 patients, the allograft was removed. Only five of the total 35 study patients (14%) lost the originally preserved epiphysis owing to complications. The mean functional score was 26 points (range, 10–30 points, with a higher score representing a better result) at final followup.

Conclusions Although the recurrence rate was high in this series, the small sample size means that even one or two fewer recurrences might have resulted in a much more favorable percentage. Because of this, future, larger studies will need to determine whether this is a safe approach, and perhaps should compare epiphyseal preservation with other possible approaches, including endoprosthetic reconstruction and/or osteoarticular allografts.

Level of Evidence Level IV, therapeutic study.

Introduction

Currently, patients with high-grade osteosarcoma treated with the combination of chemotherapy and tumor resection with adequate margins may have a survival rate greater than 70% after 5 years [3, 8]. The most common tumor resection technique used for a metaphyseal osteosarcoma of the distal femur or proximal tibia is the intraarticular resection of the distal part of the femur, proximal part of the tibia, or both [11, 23]. However, intercalary tumor resection, with preservation of the epiphysis and knee, is an alternative in patients without tumor involvement of the distal part of the femur or the proximal part of the tibia [1, 5, 7, 14, 24, 26]. The technique is possible in selected patients owing to advances in preoperative imaging [9, 10, 18–22], which allows the surgeon to determine tumor margins and plan tumor resection that preserve a patient's uninvolved epiphysis.

Some short-term results have been reported [15, 16, 25], but long-term studies analyzing oncologic outcomes are scarce [27]. Although we previously found that reconstructive complications that require second operations are to be expected [16], we suggested that approximately one of six metaphyseal osteosarcomas around the knee could be treated with appropriate oncologic margins and preservation of the epiphysis of the affected bone; however, evaluation of these patients with longer followup has not been reported.

We therefore sought to determine whether this type of resection allows acceptable limb function without increasing the risk of local recurrence or death in patients with osteosarcoma of the knee followed for 5 or more years. To address this issue, we asked the following questions: what is (1) the overall survival in patients treated with this surgical technique; (2) the percentage of local recurrence and limb survival, specifically, the incidence of recurrence in the remaining epiphysis; (3) the frequency of orthopaedic complications; and (4) the functional outcomes in patients who have undergone intercalary tumor resection.

Patients and Methods

We reviewed 223 patients with high-grade osteosarcomas of the knee treated from March 1991 to March 2008 at our institution. We included in this study all patients treated with proximal tibia or distal femur epiphyseal preservation after tumor resection, and who had reconstruction with an intercalary allograft. We excluded patients treated with resection of the entire distal femur or proximal tibia or patients who had a previous inappropriate operation owing to misdiagnosis. This left 35 patients available for our study (Table 1). During the study period, our indications for this approach included patients without metastases, with clinical and imaging response to neoadjuvant chemotherapy, that a residual epiphysis of at least 1 cm thickness could be available after a surgical margin width in bone of 10 mm was planned, and 16% of patients (35 of 223) meeting these indications were treated using this approach.

Nine tumors were located in the tibia and 26 were in the femur. There were 16 females and 19 males, with a mean age of 17 years (range, 2–50 years). The growth plate was open in 11 patients (seven patients were younger than 10 years) and we did not attempt to preserve it in these patients. Patients with limb length discrepancy were treated by distraction osteogenesis procedures if needed at skeletal maturity. A minimum followup of 5 years was required for inclusion, unless death from tumor progression occurred earlier. The duration of followup was calculated from the date of the resection to the date that the patient was last seen (for asymptomatic patients) or the date of death or amputation (for limb-survival analysis). The average followup was 9 years (range, 1–23 years, again allowing for inclusion of patient data from those who died before the 5-year minimum followup). No patient was lost to followup.

All patients were treated with neoadjuvant chemotherapy. Three patients were treated with a combination of cisplatin (100 mg/m², Weeks 0, 6, and 14), ifosfamide (3 g/m² for 2 days, Weeks 3, 11, and 17), and doxorubicin (25 mg/m² for 3 days, Weeks 3, 6, 11, 14, and 17) [4]. Surgical treatment was in the ninth week of the protocol. The remaining 32 patients were treated with a combination of ifosfamide (1.8 g/m² for 5 days, Weeks 0, 5, and 10), Adriamycin (25 mg/m² for 3 days, Weeks 0, 5, and 10), and high-dose methotrexate (12 g/m², Weeks 3, 4, 8, 9, 13, and 14) [4]. Surgical treatment occurred during the 15th week of the protocol.

Preoperatively, we evaluated all patients with MRI. Images were acquired with a 1.5-T Magnetom Vision unit (Siemens, Erlangen, Germany) at the time of the diagnosis and at the end of each chemotherapy regimen. The image acquisition protocol was made as reported previously [16]. The extent of epiphyseal involvement was calculated with

Table 1. Demographic data of the patients

Patient	Age (years)	Sex	Bone	Open growth plate	Tumor necrosis (percent)	Followup (months)	Epiphysis preservation	Complication	MSTS	Normal knee function	Use of external support
1	18	F	T	No	≥ 90	276	Yes	No	27	Yes	No
2	24	M	T	No	≥ 90	123	No	Infection	10	No	Yes
3	9	F	F	Yes	≥ 90	184	Yes	Fracture	27	No	No
4	16	M	F	No	≥ 90	189	Yes	Fracture	20	No	No
5	18	F	F	No	≥ 90	26	Yes	No	NA	NA	NA
6	40	F	F	No	≥ 90	174	Yes	Fracture	29	Yes	No
7	21	M	F	No	≥ 90	156	No	Fracture	20	No	Yes
8	17	F	F	No	≥ 90	166	Yes	No	29	Yes	No
9	14	F	T	No	≥ 90	162	Yes	Fracture	29	Yes	No
10	18	M	T	No	≥ 90	161	Yes	Fracture	25	Yes	No
11	15	F	T	No	≥ 90	147	Yes	LR	30	Yes	No
12	13	F	T	Yes	≥ 90	134	Yes	Fracture	29	Yes	No
13	17	F	F	No	≥ 90	153	Yes	No	28	Yes	No
14	18	F	F	No	≥ 90	129	No	Fracture	22	No	No
15	11	F	F	Yes	≥ 90	132	Yes	No	30	Yes	No
16	50	F	F	No	< 90	59	No	LR	NA	NA	NA
17	16	M	T	No	≥ 90	132	Yes	Nonunion	30	Yes	No
18	16	M	T	No	< 90	129	Yes	No	29	Yes	No
19	16	M	F	No	≥ 90	134	Yes	Fracture	30	Yes	No
20	22	M	F	No	≥ 90	113	Yes	Nonunion	25	No	No
21	12	M	F	Yes	≥ 90	121	Yes	Fracture	27	No	No
22	21	M	F	No	< 90	23	Yes	No	NA	NA	NA
23	9	M	F	Yes	≥ 90	21	Yes	LR	NA	NA	NA
24	15	F	F	No	< 90	92	Yes	No	30	Yes	No
25	6	M	F	Yes	< 90	87	Yes	No	28	No	No
26	8	F	F	Yes	≥ 90	88	Yes	No	27	No	No
27	17	M	T	No	≥ 90	85	Yes	Infection	29	Yes	No
28	8	M	F	Yes	≥ 90	79	Yes	Nonunion	25	No	No
29	37	F	F	No	≥ 90	85	Yes	No	30	Yes	No
30	5	M	F	Yes	≥ 90	81	Yes	Fracture	28	No	No
31	19	M	F	No	< 90	76	Yes	No	27	Yes	No
32	13	F	F	No	≥ 90	62	Yes	No	28	Yes	No
33	10	M	F	Yes	≥ 90	60	Yes	No	28	No	No
34	13	M	F	No	≥ 90	60	Yes	No	28	Yes	No
35	2	M	F	Yes	≥ 90	34	Yes	No	NA	NA	NA

T = tibia; F = femur; LR = local recurrence; MSTS = Musculoskeletal Tumor Society functional score; NA = not available.

coronal, sagittal, and axial images defining the edge of the tumor as the point in which marrow signal intensity changed from normal to abnormal. Patients were evaluated according to the following criteria: (1) the assessment of tumor response or progression as assessed by MRI; (2) the age of the patient and potential for skeletal growth; (3) the distance between the articular joint cartilage and the tumor as assessed by MRI of 2 cm or more, to obtain a bone width margin of 10 mm and a remaining residual epiphysis of 1 cm (Fig. 1); and (4) a sufficient amount of epiphysis

preserved to allow fixation of the osteotomy junction [16]. Tumors with evidence of clinical response, such as pain and mass reduction, and evidence of necrosis and reduction of soft tissue mass on MR images during chemotherapy were considered for this procedure. In all patients, operative treatment consisted of resection of the tumor and insertion of an allograft segment tailored to fit the bone defect using a technique previously described [17]. After the operations, the histologic margins were negative in all patients. All patients had a margin width in bone of at least

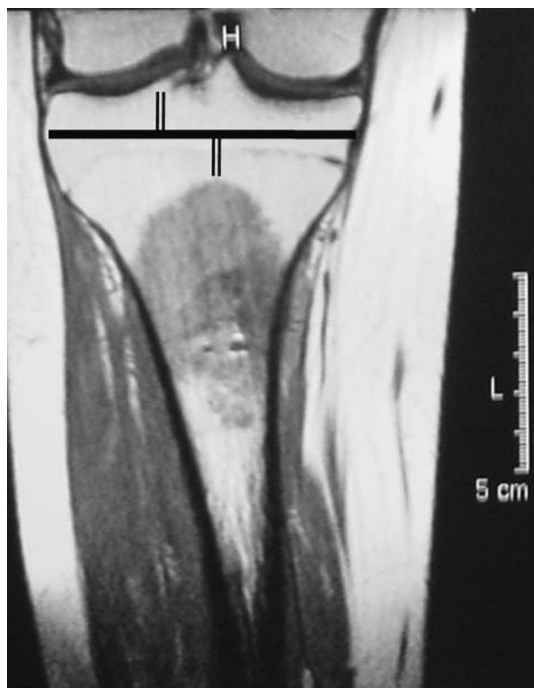


Fig. 1 A coronal MR image of the right proximal tibia shows how the transepiphyseal osteotomy was planned in a patient with an osteosarcoma. The horizontal black line shows the planned osteotomy in the epiphysis, there are two 1-cm vertical black lines on either side of the osteotomy (the proximal line shows the remaining proximal tibia, and the distal one shows the 1 cm margin planned to be obtained).

10 mm. Although all patients showed clinical response and response on MR images to preoperative chemotherapy, 29 had tumor necrosis of 90% or greater (Table 1) and six had necrosis less than 90%.

Patients' overall survival and limb survival were estimated using the Kaplan–Meier method [13]. Oncologic complications, such as local recurrence and tumor progression, were evaluated. We analyzed limb survival, the number of secondary amputations, and the number of patients in whom the preserved epiphysis eventually was maintained. We used SPSS 17.0 for Windows (SPSS, Inc, Chicago, IL, USA) for statistical analyses.

Functional evaluation of the patients was performed using the revised 30-point functional classification system established by the International Society of Limb Salvage and the Musculoskeletal Tumor Society (MSTS) [6]. The functional score measured six parameters: pain, function, emotional acceptance, use of walking supports, walking ability, and gait. Each parameter is given a value ranging from 0 to 5, according to specific criteria. The individual scores are added together to obtain an overall functional score, with a maximum of 30 points, which then is expressed as a percentage of normal, with 30 points being defined as normal function. A score of 23 points or greater

is considered an excellent functional result, 15 to 22 points is a good result, 8 to 14 points is a fair result, and less than 8 points is a poor result [6].

Results

The overall Kaplan–Meier survival for our study population was 86% at 5 years and 10 years (95% CI, 73%–99%) (Fig. 2). At the final followup, 30 patients continued to be disease-free and five had died of disease (three with $\geq 90\%$ tumor necrosis and two with $< 90\%$ tumor necrosis).

Three patients (9%; 95% CI, 0%–19%) had a soft tissue local recurrence (two with $\geq 90\%$ tumor necrosis and one with $< 90\%$ tumor necrosis) (Table 1) and two of them died of pulmonary metastases. Of the three patients with local recurrences, one was treated with amputation because of contact with neurovascular structures and died of disease 30 months from discovery of the recurrence. The remaining two patients were treated with resection of the local soft tissue recurrence. One patient is alive without detectable disease at 120 months after resection of the recurrence and the other died 11 months after resection. Of these three patients, one had had a previous pathologic fracture at the time of the original diagnosis. No patient had a local recurrence in the preserved epiphysis. The Kaplan–Meier limb survival was 97% at 5 years and 10 years (95% CI, 89%–100%). In total, five patients lost the originally saved epiphysis owing to fracture (three patients), amputation (one patient), or infection (one patient).

Of the 35 patients in the study, 16 (46%; 95% CI, 22%–70%) achieved healing without orthopaedic or oncologic complications. A second surgical procedure was performed in 19 patients, three to treat oncologic complications (three local recurrences) and 16 to treat orthopaedic complications, including 11 fractures, three diaphyseal nonunions, and two deep infections. In nine (26%) patients, the allograft was removed because of orthopaedic complications (seven fractures and two infections). Kaplan–Meier allograft survival was 73% at 5 years (95% CI, 58%–88%) and 68% at 10 years (95% CI, 50%–86%) (Fig. 3). In seven of the 11 fractures, the allografts were removed and treated with a new reconstruction. All were localized in the femur and four were treated with another intercalary graft to preserve the original epiphysis. The remaining three fractures were treated with distal femur endoprostheses (two patients) or an osteoarticular allograft (one patient), sacrificing the originally preserved epiphysis. Four of the 11 fractures were nondisplaced; three were tibial fractures and one was located in the femur. All were treated with a new osteosynthesis using autogenous bone graft. In all three diaphyseal nonunions, one operation in which the

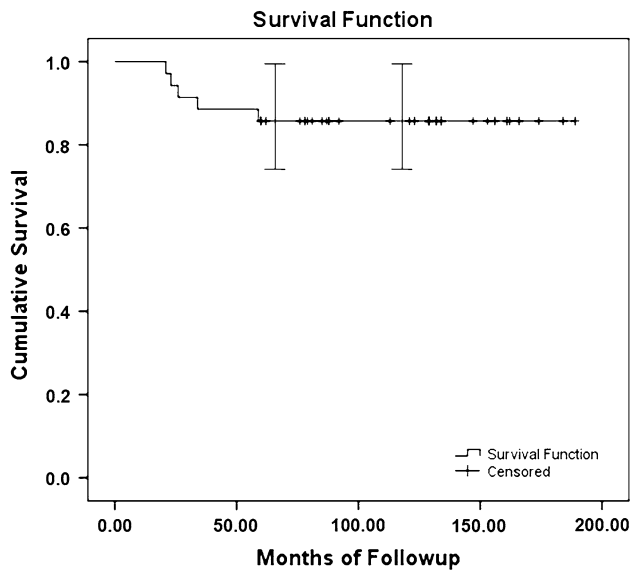


Fig. 2 A graph shows a Kaplan-Meier curve for survival of the study patients. The overall survival rate for patients was 86% at 5 years and 10 years (95% CI, 73%–99%).

internal fixation was replaced and autogenous graft was added to the site resulted in union at the host-donor junction in a mean of 4 months. Two patients had acute deep infections, which were treated with removal of the allograft and implantation of a temporary antibiotic-impregnated cement spacer. After infection control one patient finally was treated with a new intercalary allograft (Fig. 4) and the other had reconstruction with a proximal tibia allograft-prosthesis composite, losing the originally saved epiphysis.

The 30 patients available for functional evaluation had a mean functional score of 26 points (range, 10–30 points) (Table 1). Two patients needed some kind of support to walk, whereas the other 28 were able to walk unaided. Eighteen patients achieved normal knee flexion and extension. The 26 patients who had the epiphysis preserved had a mean functional score of 28 points.

Discussion

Tumor resection surgery with preservation of the epiphysis in patients with metaphyseal osteosarcoma is a technique that has been attempted in recent years. This is likely attributable to better imaging technologies and more experience with limb-preservation techniques. However, there is a paucity of literature regarding the long-term oncologic and orthopaedic results of this approach [24]. We therefore sought to evaluate (1) the overall survival in patients treated with this surgical technique; (2) the percentage of local recurrence and limb survival, specifically, the incidence of recurrence in the remaining epiphysis;

(3) the frequency of orthopaedic complications; and (4) the functional outcomes in patients treated with this approach.

We acknowledge some limitations to our study. It was a retrospective study with a small number of patients. Given the relative rarity of the disease and the unique surgical treatment for each individual, it would be difficult to obtain a larger series at one center, however, to our knowledge, ours is one of the largest studies for this type of bone tumor resection and it presents long-term oncologic and orthopaedic outcomes. Another limitation is that we did not analyze patients who met reasonable indications for an epiphyseal-sparing approach but were treated with other approaches (prostheses or osteoarticular grafts) because of the lack of evidence of clinical or MRI response, or both, to compare survival or local recurrence.

Overall survival in our series was 86%. This survival rate is higher compared with other series of patients with high-grade osteosarcomas [3, 8], however, for this type of surgical resection, patients were carefully selected. One of the main indications for this method is clinical and imaging response of the patient to neoadjuvant chemotherapy. Conversely, if a patient did not respond during neoadjuvant chemotherapy, this type of resection would be contraindicated. However, although we selected these patients with clinical and imaging parameters, six were not good responders, but the margins obtained were free of tumor and no other surgical approach was performed. Andreou et al. [2] reported that patients participating in a study fared significantly better ($p < 0.0001$) than those who were only registered and followed prospectively. This could be the cause of the higher patient survival in our series because although six patients were histologically poor responders, they could have other favorable characteristics such as small tumor size, adequate biopsy, or absence of soft tissue infiltration.

In our series, we observed three (9%) local recurrences. Only one patient was treated with amputation for a local recurrence, giving us a limb-survival rate of 97%, a percentage of limb salvage similar to those of other published series [5, 16]. Two other local recurrences were treated with an oncologic resection with limb preservation. All recurrences were in soft tissue, and none was in the remaining original epiphysis. Although the recurrence rate was high in our series, the small sample size means that even one or two fewer recurrences might have resulted in a much more favorable percentage. Canadell et al. [5] performed transepiphyseal resection in 12 high-grade osteosarcomas and had one local recurrence in their series. Our incidence of local recurrences is similar to that observed in other patients with osteosarcomas treated with limb-sparing surgery with other techniques [2, 5, 8, 12, 14]. Ferrari et al. [8] reported 18 local recurrences (8%) in 230 patients who had conservative surgery. Although there is

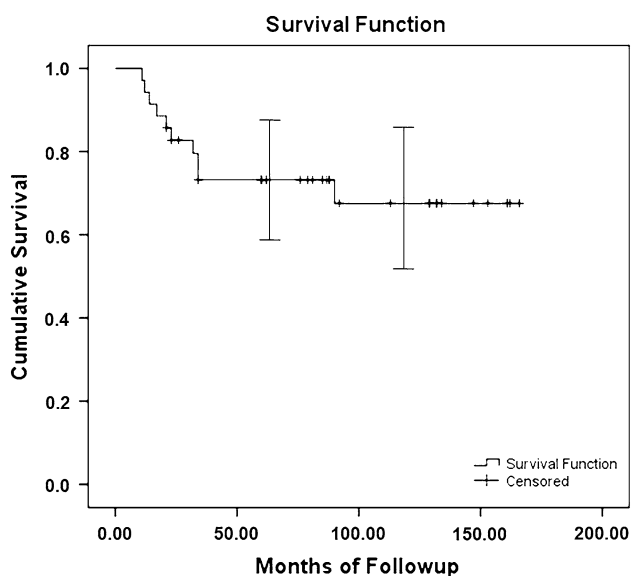


Fig. 3 The graph shows a Kaplan-Meier curve for survival of allografts. The overall survival rate for the 35 allografts was 73% at 5 years (95% CI, 58%–88%) and 68% at 10 years (95% CI, 50%–86%).



Fig. 4A–C A 17-year old male patient had an osteosarcoma of the right proximal tibia. He underwent reconstruction with an intercalary tibia allograft after transepiphyseal resection of a metadiaphyseal osteosarcoma. (A) An AP radiograph of the right proximal tibia obtained immediately after resection of the tumor and reconstruction with an allograft shows fixation of the allograft to the host bone with a medial buttress proximal plate and two screws in the remaining epiphysis. (B) An AP radiograph of the right proximal tibia 1 year after reconstruction shows a temporary antibiotic-impregnated cement spacer that replaced the original allograft owing to a deep infection. (C) Seven years postoperatively, the patient's AP radiograph of the right tibia is shown. The patient underwent reconstruction with a second allograft with a new lateral long plate (proximal tibia locking compression plate) that covers both osteotomies and addition of a short medial plate in the distal osteotomy.

no consensus regarding what constitutes an appropriate margin for resection of an osteosarcoma with a good response to chemotherapy, in our series, leaving a margin

of at least 1 cm, we observed no local recurrences in the remaining bony epiphysis. Andreou et al. [2] reported that limb-sparing procedures were associated with a higher local recurrence rate (7.5%), with no difference in disease-specific survival ($p = 0.118$). They also found that surgical margin width in bone did not correlate with the local recurrence rate, either in the group as a whole ($p = 0.126$) or in subgroup analyses of limb-sparing procedures only ($p = 0.692$), margin width of 10 mm or less only ($p = 0.223$), 20 mm or less only ($p = 0.379$), or when comparing a width of 10 mm or less with a width of 11 to 20 mm. Jeon et al. [12] analyzed 35 local recurrences in 445 osteosarcomas (7.8%), and reported no relation between the adequacy of soft tissue margin and local recurrences in a corresponding area. They observed local recurrence located away from the initial tumor or in patients who had whole muscle compartment resections. They suggested that in the soft tissues, poor responders might have different local tumor spread mechanisms from those of good responders. Recurrence could be more dependent on vascular or lymphatic pathways rather than by direct infiltration of the muscle compartment.

Sixteen of our patients (46%) had orthopaedic complications related to the reconstruction. The main complication was fracture of the allograft in 11 patients (31%). Yu et al. [27] analyzed five patients with preservation of the epiphysis after resection of high-grade osteosarcomas with a minimum followup of 5 years, and they described three fractures (66%) in their series. Weitao et al. [25] analyzed 15 patients with epiphysis-preserving operations for treatment of lower-limb malignant bone tumors, with a minimum followup of 2 years who had reconstruction with an intercalary allograft. They observed 13 patients with delayed union (87%), two with resorption of the graft (13%), and one with infection (7%). We had only three patients with non-union (9%), but our infection rate was similar to their reported rate (6%; two of 35 patients).

Allograft survival was 73% with a mean functional score of 26 for our patients. Normal knee flexion and extension was achieved by 18 patients and 28 patients were able to walk unaided after surgery. These results are comparable with those of previous studies of reconstruction of bone defects if the epiphysis is preserved [7, 23–27]. Yu et al. [27] evaluated five patients in whom the epiphysis was preserved after resection of osteosarcoma of the distal femur; their patients were followed for more than 5 years. The mean functional score in their series was 25.6 points. Weitao et al. [25] analyzed 15 patients with epiphysis-preserving operations for treatment of lower-limb malignant bone tumors. Normal knee flexion and extension were achieved by 14 patients and all were able to walk unaided 24 months after surgery. Yao et al. [26] evaluated six patients with distal femur osteosarcoma who underwent

epiphysis-preserving operations. The final functional MSTS score for their patients was 27.20 ± 1.92 .

Preservation of the epiphysis is a reasonable alternative in selected patients with a metaphyseal osteosarcoma located at the knee, with adequate long-term survival. The advantages of this technique are preservation of a normal joint in a young patient, the possibility of avoiding joint complications seen with osteoarticular grafts (need for conversion to TKA at some point, joint instability) and endoprostheses (loosening, revisions). However, the recurrence rate was high in our series with a selected group of patients. Crucial factors in selecting patients for this technique are the ability to obtain adequate margins and good response to neoadjuvant chemotherapy. It is possible that poor responders have different local tumor spread mechanisms from those of good responders. Although we selected patients with clinical and imaging parameters, a small number of the patients were good responders, and might have been better served with another surgical approach. Future studies with more patients are needed to determine whether this is a safe approach, and perhaps should compare epiphyseal preservation with other possible approaches, including endoprosthetic reconstruction and/or osteoarticular allografts.

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