■ ONCOLOGY

Transepiphyseal resection for osteosarcoma in patients with open physes using MRI assessment

SAFETY AND CLINICAL OUTCOMES

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Aims

For paediatric and adolescent patients with growth potential, preservation of the physiological joint by transepiphyseal resection (TER) of the femur confers definite advantages over arthroplasty procedures. We hypothesized that the extent of the tumour and changes in its extent after neoadjuvant chemotherapy are essential factors in the selection of this procedure, and can be assessed with MRI. The oncological and functional outcomes of the procedure were reviewed to confirm its safety and efficacy.

Methods

We retrospectively reviewed 16 patients (seven male and nine female, mean age 12.2 years (7 to 16)) with osteosarcoma of the knee who had been treated by TER. We evaluated the MRI scans before and after neoadjuvant chemotherapy for all patients to assess the extent of the disease and the response to treatment.

Results

The mean follow-up period was 64.3 months (25 to 148) after surgery and no patients were lost to follow-up. On MRI evaluation, 13 tumours were near but not in contact with the physes and three tumours were partially in contact with the physes before neoadjuvant chemotherapy. Bone oedema in the epiphysis was observed in eight patients. After neoadjuvant chemotherapy, bone oedema in the epiphysis disappeared in all patients. In total, 11 tumours were not in contact and five tumours were in partial contact with the physes. The postoperative pathological margin was negative in all patients. At the last follow-up, 12 patients were continuously disease-free and three had no evidence of disease. One patient died due to the disease. Functionally, the patients with retained allograft or recycled autograft had a mean knee range of flexion of 126° (90° to 150°). The mean Musculoskeletal Tumor Society functional score was 27.6 (23 to 30).

Conclusion

TER is an effective limb-salvage technique for treating malignant metaphyseal bone tumours in paediatric and young osteosarcoma patients with open physes when a good response to chemotherapy and no progression of the tumour to the epiphysis have been confirmed by MRI.

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Introduction

Osteosarcoma is the most common primary malignant tumour of the bone, and most frequently involves the site around the knee. The lesion usually occurs in the metadiaphysis during the early stages and subsequently spreads over the epiphysis in the later stages.[1] With modern treatment protocols for osteosarcoma, the survival rate for patients with high-grade tumours treated with a combination of wide excision and chemotherapy has exceeded 70% at five years. In addition to the improvement in life expectancy, the functionality of the limb and enhanced quality of life comprise the main goals of treatment.[2]

Transepiphyseal resection (TER) has been considered an ideal strategy due to its preservation of the native knee joint, which precludes many joint complications associated with endoprostheses and

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Table I. Demographic data of the patients.

N	Age, yrs	Sex, M/F	Site	Grade	Tumour size, mm	Resected bone size, mm	Graft type* (length, mm)	Neoadjuvant chemo	Follow-up, mths	Final status	MSTS score	Complication
1	13	M	PT	High	49	105	Allobone (105)	Yes	148	CDF	30	None
2	9	F	DF	High	68	165	Allobone (160)	Yes	125	CDF	28	Fracture
3	15	F	DF	High	52	150	Allobone (150)	Yes	105	CDF	30	None
4	13	F	DF	High	240	396	APC (396)	Yes	103	NED	25	None
5	14	F	DF	High	55	310	Autobone, pasteurization (310)	Yes	75	DOD	28	None
6	15	M	DF	High	107	164	Allobone (164)	Yes	82	NED	25	Nonunion
7	16	M	DF	High	76	170	Allobone (170)	Yes	54	CDF	25	Nonunion/infection
8	11	F	DF	High	52	80	Allobone (80)	Yes	47	CDF	29	Nonunion
9	13	F	DF	High	35	140	Allobone (143)	Yes	38	CDF	24	None
10	13	M	PT	High	75	169	Allobone (169)	Yes	31	CDF	28	Infection
11	7	F	DF	High	49	103	Allobone (103)	Yes	34	CDF	28	None
12	13	F	DF	High	53	169	Allobone (170)	Yes	44	CDF	29	None
13	12	F	DF	High	48	71	Autobone pasteurization (71)	Yes	26	CDF	23	None
14	6	M	PT	High	49	118	Autobone, frozen (118)	Yes	25	CDF	30	None
15	9	M	DF	High	118	275	Allobone (275)	Yes	55	NED	30	None
16	14	M	DF	High	120	210	Allobone (210)	Yes	37	CDF	30	None

*Allobone: donor allograft; Autobone, pasteurization: autograft recycled by pasteurization; Autobone, frozen: autograft recycled by liquid nitrogen.
APC, allograft-prosthesis composite; CDF, continuously disease-free; DF, distal femur; F, female; M, male; MSTS, Musculoskeletal Tumor Society functional Score; N, number; NED, no evidence of disease; PT, proximal tibia; TF, total femur.

osteoarticular allografts.[3] However, the controversial issue associated with this procedure is the narrow margin of clearance when the tumour invades the epiphysis. A sufficient surgical margin is a well-known independent prognostic factor for local recurrence.[4] The growth plate is considered to be a better barrier than the same thickness of other tissues.[5,6] MRI is an effective tool for assessing the epiphyseal extension of the tumour with high specificity and sensitivity.[7,8] Additionally, good response to neoadjuvant chemotherapy is another prognostic factor for local recurrence.[9-13] Our hypotheses were as follows: firstly, that TER of the distal femur and proximal tibia can be performed in osteosarcoma patients with open physes when there is no obvious tumour invasion to the epiphysis and when the changes in the lesion after neoadjuvant chemotherapy indicate a good response; and secondly, that MRI is a safe and reliable tool for assessing the extent of, and changes in, the lesion before and after neoadjuvant chemotherapy. We specified the indications for TER as the absence of tumour involvement in the epiphysis on initial MRI and no bone marrow oedema observed in the epiphysis after neoadjuvant chemotherapy. We reviewed the oncological and clinical outcomes, including any complications, to assess the safety and efficacy of this procedure.

Methods

After institutional review board approval, we retrospectively reviewed the medical records and radiographs of 97 consecutive patients with osteosarcoma of the distal femur or proximal tibia who had undergone limb salvage surgery between 2005 and 2016. Among them, we excluded the patients who had closed physes or whose osteosarcoma was evidently invading the epiphysis with MRI. In total, we identified 16 patients (seven male and nine female) with a mean age at operation of 12.2 years (7 to 16) with open physes who underwent TER for metaphyseal osteosarcoma of the distal femur or proximal tibia after receiving neoadjuvant chemotherapy.

Indications for TER. We performed TER in patients with osteosarcoma which had occurred in the presence of an open growth plate providing that the initial MRI showed no obvious tumour invasion into the epiphysis. When the tumour was abutting or close to the physis, TER was considered as an appropriate option and serial MRI after each cycle of neoadjuvant chemotherapy was assessed. If the lesion did not invade epiphysis on MRI after neoadjuvant chemotherapy, we performed TER. When bone marrow oedema was noted at the epiphysis, serial MRIs were conducted to assess the change of the oedema. When bone marrow oedema was absent at the epiphysis, on MRI after neoadjuvant chemotherapy, TER was performed. TER was not indicated when a tumour was noted on the initial MRI to have extended to the epiphysis through the growth plate.

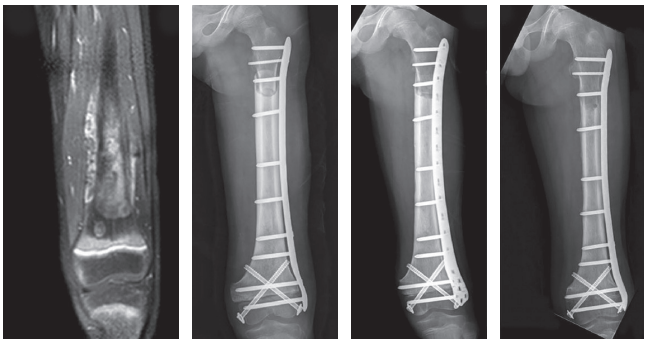
Evaluation of tumour extent and response of neoadjuvant chemotherapy using MRI. We used MRI to assess the tumour extent and the change of the lesion after neoadjuvant chemotherapy. The utility of MRI for this purpose has been reported previously and shown to be superior to other modalities.[7,8,13-15]

Surgical technique of TER. When the tumour was not in contact with the physis, osteotomy was performed through the epiphysis just distal to the physis in the distal femur and just proximal to the physis in the proximal tibia, under the guidance of intraoperative fluoroscopy. When the tumour was touching the physis, we performed intra-epiphyseal osteotomy at least 3 mm from the physis to secure space for internal screw fixation. In the diaphysis, the osteotomy level was decided with a

Table II. Assessment of appropriateness of the indications of transepiphyseal resection with neoadjuvant chemotherapy using MRI and postoperative histological results.

n	Age, yrs	Sex, M/F	Location	Contact with the physis		Bone marrow oedema in the epiphysis		Pathological margin	Margin, mm		Tumour necrosis, %	Huvos Grade
				Before	After	Before	After		Epiphysis	Diaphysis		
1	13	M	PT	Yes	No	Present	Absent	Negative	6	50	95	3
2	9	F	DF	No	No	Present	Absent	Negative	5	70	100	4
3	15	F	DF	No	No	Present	Absent	Negative	8	50	95	3
4	13	F	DF	Yes	Yes	Present	Absent	Negative	20	30	95	3
5	14	F	DF	No	No	Absent	Absent	Negative	20	30	100	4
6	15	M	DF	No	No	Absent	Absent	Negative	10	40	90	3
7	16	M	DF	No	No	Present	Absent	Negative	6	85	95	3
8	11	F	DF	Yes	Yes	Present	Absent	Negative	3	29	100	4
9	13	F	DF	No	No	Absent	Absent	Negative	19	162	100	4
10	13	M	PT	No	Yes	Absent	Absent	Negative	12	85	100	3
11	7	F	DF	Yes	Yes	Present	Absent	Negative	3	35	100	4
12	13	F	DF	No	No	Present	Absent	Negative	48	59	≥ 95	3
13	12	F	DF	No	Yes	Absent	Absent	Negative	5	50	100	4
14	6	M	PT	No	No	Absent	Absent	Negative	10	35	60	2
15	9	M	DF	No	No	Absent	Absent	Negative	11	42	85	2
16	14	M	DF	No	No	Absent	Absent	Negative	24	28	90	3

*Huvos system: Grade 1: little or no evidence of necrosis; Grade 2: necrosis of 50% to 90%; Grade 3: necrosis between 90% to 99%; finally, Grade 4: 100% necrosis.
DF, distal femur; F female; M, male; N, number; PT, proximal tibia.



a b c d

Fig. 1

Radiographs of the transepiphyseal resection with intercalary reconstruction in a nine-year-old boy (Patient 15) who was diagnosed with high-grade osteosarcoma. a) A coronal T1-weighted MRI scan shows the bone extension in the metaphyseal area of the distal femur. Plain radiographs taken b) immediately and c) at four and d) 28 months after allograft reconstruction, respectively.

sufficiently wide margin according to the conventional surgical margin system based on MRI. When allografts were used these were selected based on a comparison of the patient's radiographs with those of the donor, to achieve the closest anatomical match. To reinforce the fixation and compress the host epiphysis-allograft junction, cannulated or cancellous screws were inserted from the host epiphyseal side to the allograft in oblique fashion. A locking compression plate (LCP) (DePuy Synthes, Raynham, Massachusetts, USA) was then applied and secured with locking screws. In addition, according to the findings, several methods were applied to enhance the fixation and prevent complications, such as the telescopic mating technique to maximize the bony contact area,[16] use of additional plates, or an intramedullary nail to sustain firm fixation.[17,18]

Assessment of the oncological and clinical outcomes. Oncological outcomes were assessed by the surgical margins and histological evaluation of the response to neoadjuvant chemotherapy using Huvos grading and survival rate.[19] The Huvos grading system is based on the tumour cell necrosis rate and consists of four grades: grade 1: rare necrosis; grade 2: less than 50% to 90% necrosis; grade 3: 90% or more necrosis; and grade 4: 100% necrosis. Grades 1 and 2 were considered to indicate a poor therapeutic response and grades 3 and 4 a good therapeutic response.[19] Regular postoperative follow-up included a radiograph imaging, bone scanning, and chest CT every three months for the first two years after surgery and every six months thereafter. Clinical outcomes were evaluated based on the Musculoskeletal Tumor Society (MSTS) scoring system,[20] knee range of movement (ROM), leg length discrepancy (LLD), and postoperative complications. ROM was measured in the outpatient clinic by two oncological orthpaedic surgeons (KYS, KHS) and LLD was measured with teleradiograph or Bell-Thompson radiograph by KYS. All the MRI scans were reviewed by one radiologist in our institute. For internal validation, two oncological orthopaedic surgeons associated with the study (KYS, KHS) reviewed the images again.

Statistical analysis. Graft survival was estimated from the date of surgery to the date of revision or date of last follow-up and assessed using Kaplan-Meier method. All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS v. 24.0, IBM, Armonk, New York, USA). A p-value < 0.05 was considered statistically significant.

Results

The patients. The mean follow-up period was 64.3 months (25 to 148) after surgery and no patients were lost to follow-up. The location of the tumour was the distal femur in 13 patients and the proximal tibia in three patients (Table I). On histological

Table III. Evaluation of leg length discrepancy in the cohort. Minus sign indicates the amount of decrease in length on the affected side of the limbs.

N	Age, yrs	Sex, M/F	Location/orientation	LLD of the femur, mm	LLD of the tibia, mm	Total LLD, mm	Follow-up from surgery, mths
1	13	M	PT/L	-18.2	+ 2.7	-15.5	103
2	9	F	DF/L	-18.2	+ 2.0	-16.2	125
3	15	F	DF/L	-21.7	+ 0.5	-22.3	86
4	13	F	DF/R	-20.3	+ 1.7	-18.5	113
5	14	F	DF/R	+ 8.9	+ 3.8	+ 12.8	26
6	15	M	DF/L	-37.6	-2.3	-40.0	82
7	16	M	DF/L	-9.7	+ 2.3	-7.4	54
8	11	F	DF/R	+ 0.4	-13.1	-12.7	47
9	13	F	DF/R	-10.5	-2.5	-13.1	38
10	13	M	PT/L	-1.6	-3.1	+ 4.8	15
11	7	F	DF/L	-5.4	+ 1.2	-4.1	34
12	13	F	DF/L	-4.4	-5.1	-9.6	44
13	12	F	DF/L	-1.9	-0.1	-2.0	26
14	6	M	PT/R	-3.9	-8.2	+ 12.2	25
15	9	M	DF/L	-34.3	+ 8.5	-25.8	51
16	14	M	DF/L	+ 1.0	-14.9	-13.8	35

DF, distal femur; F, female; L, left; LLD, leg length discrepancy; M, male; PT, proximal tibia; R, right.

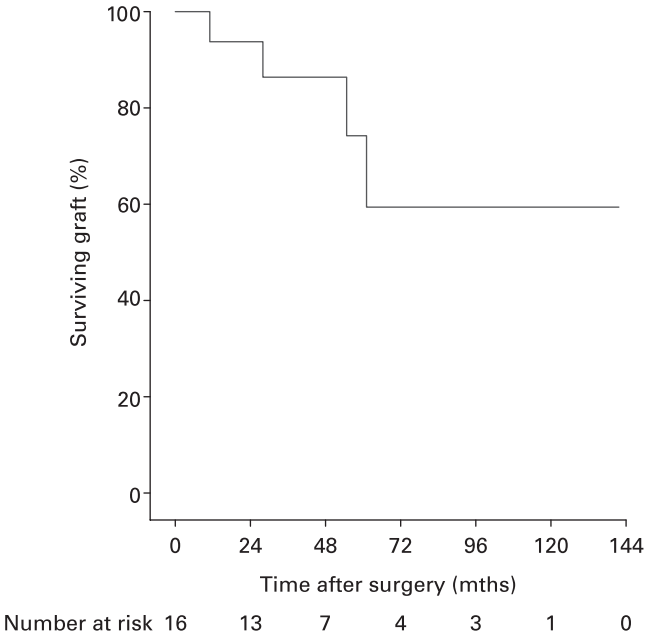


Fig. 2

Kaplan-Meier curve for survival of the allograft. The overall survival rate of allografts was 74.2% (95% CI 67.4% to 80.3%) at five years.

examination, all the tumours were diagnosed as high-grade osteosarcoma. One patient (Patient 4) had osteosarcoma with entire femoral involvement without distal epiphysis invasion.

Assessment of the response to neoadjuvant chemotherapy by MRI. On MRI evaluation, 13 tumours were near, but not in contact with, the physes and three tumours (18.8%) were in partial contact with the physes before neoadjuvant chemotherapy. Bone oedema in the epiphysis was observed in eight patients. After neoadjuvant chemotherapy, the bone oedema in the epiphysis resolved in all patients (Table II) (Figure 1). In all, 11 tumours were not in contact and five tumours were in partial contact with the physes. The resection margin was clear of tumour in all patients.

On histological analysis according to the Huvos grading system, 14 of the 16 patients were good responders: seven patients were grade 4, seven patients were grade 3, and two patients were grade 2. One patient (case 14) showed 60% necrosis following neoadjuvant chemotherapy.

Oncological outcomes. The overall survival rate was 15/16 at the last follow-up. All surviving patients were continuously disease-free (CDF) or no evidence of disease (NED). None of the patients developed local recurrence. In total, 12 patients had no metastases at the time of diagnosis and continued to be disease-free. Three patients (Patients 4, 5, and 15) had lung metastases at the time of initial diagnosis and one patient (Patient 6) developed lung metastases 14 months after surgery. All of these patients underwent metastasectomy. One patient (Patient 5) died of neutropenia-related septic shock. The other three patients were living with NED at the last follow-up.

Clinical outcomes. No patient required an endoprosthesis. Allograft (n = 13), pasteurized autograft (n = 2), and frozen autograft (n = 1) were used for reconstruction using a mean length of 174.6 mm (71 to 396). The mean MSTS functional score was 27.6 out of 30 (23 to 30, Table I). The mean total LLD of the lower limb at the mean follow-up of 56.5 months was 10.7 mm (12.8 to 40.0, Table III). The mean range of flexion of the knee joint was 126° (90° to 150°) at the last follow-up.

Complications. Five patients with complications required a secondary surgery: nonunion (n = 2), deep infection only (n = 1), nonunion and subsequent deep infection (n = 1), and graft fracture (n = 1). All nonunions occurred at the diaphyseal osteotomy site, and one patient achieved bone union after a second surgery without removing the allograft. For the two patients with deep infection, one graft was replaced with a vascularized fibular graft; the other patient with concurrent nonunion and deep infection underwent revision surgery with a new allograft after staged treatment using antibiotic-loaded cement insertion as the patient refused both an endoprosthesis and a

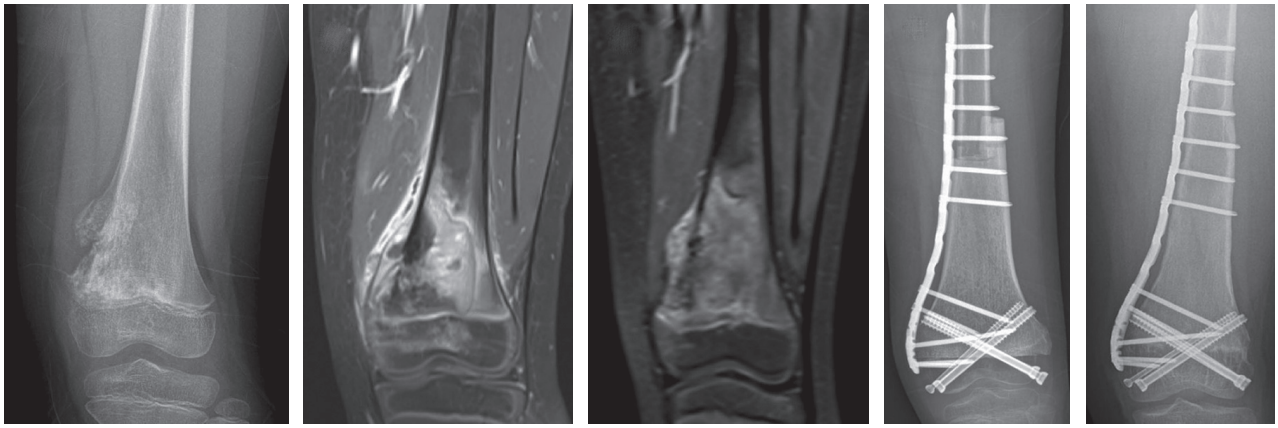


Fig. 3

Radiographs of the transepiphyseal resection with intercalary reconstruction in a seven-year-old girl (Patient 11) who was diagnosed with high-grade osteosarcoma. a) Plain radiograph after neoadjuvant chemotherapy, b) enhanced T1-weighted MR image taken before chemotherapy, c) enhanced T1-weighted MR image taken after neoadjuvant chemotherapy showed an absence of bone marrow oedema in the epiphysis, d, e) plain radiographs taken postoperatively and at three-year follow-up each showed bone union at both osteotomy sites. The patient had full range of knee joint motion.

vascularized fibular graft procedure. In the patient with graft fracture (Patient 2), the allograft fractured five years after the surgery and a vascularized fibular grafting was performed. The overall graft Kaplan-Meier survival rate of the 16 intercalary allografts or recycled autografts was 74.2% (95% CI 67.4 to 80.3) at five years. In four patients, graft removal was performed due to deep infection (n = 2), graft failure (n = 1), and graft fracture (n = 1) (Figure 2).

Discussion

The standard treatment for the removal of malignant metaphyseal bone tumours is wide excision, with various reconstruction methods including biological and non-biological reconstruction. When the tumour is located close to the growth plates, TER can save the epiphysis and is therefore advantageous in terms of preserving knee function. In the present study, the mean MSTS functional score was 27.6 (23 to 30) and the mean knee range of flexion was 126° (90° to 150°). We assessed LLD of the lower limb in our cohort and the mean LLD was 10.7 mm (12.8 to 40.0). (Table III) Our results suggest that TER is a viable option if the extent of disease does not transgress the epiphysis and the tumour shows a good response to neoadjuvant chemotherapy.

This study has some limitations. First, the small size of the cohort from a single institution may inevitably limit the interpretation of the results. A larger sample size in a multi-institutional study may be necessary to validate the results of this study. Secondly, the follow-up period is short. Only six out of 16 patients were followed up more than five years. In spite of successful bone union and survival result, long-term follow-up of the cohort regarding oncological outcome and graft survival should be assessed. Thirdly, regarding the assessment of LLD, we had difficulty in fully assessing the effects of TER. In terms of revision, one patient (Patient 6) underwent revision surgery and received a total joint arthroplasty at four years and seven months after the primary surgery. We measured the LLD at the last moment the patient maintained his native knee joint. In addition, we generally attempted to lengthen the affected limb during reconstruction to minimize the final LLD, there were three patients (Patients 5, 10, and 14) in whom the affected limb was longer than the contralateral limb at the time of measurement. When we exclude these three patients, the final mean LLD was 15.5 mm (2.0 to 40.0), which is still acceptable. Fourthly, the retrospective design of this study might have introduced selection bias.

To undertake TER safe margins after resection and an accurate assessment of the response to neoadjuvant chemotherapy should be guaranteed. It has been shown that inadequate surgical margins and a poor response to neoadjuvant chemotherapy are factors that independently increase the risk of local recurrence.[4] Our results showed that TER is a safe procedure when the extent of tumour and response to neoadjuvant chemotherapy were accurately assessed with MRI. Regarding the appropriate margin of resection, Li et al[21] and Bispo Júnior and Camargo[22] suggested resection margins of 5 mm and 2 mm, respectively, and showed that there were no differences in the local recurrence rate between the group in which the suggested margins were achieved and the group in which they were not achieved. In our study, the mean surgical margin was 13.1 mm from the epiphysis. The two patients (Patients 8 and 11) with the narrowest margins (3 mm) had no local recurrence at the last follow-up, which was likely due to the 100% necrosis rate (Figure 3).

Good response to neoadjuvant chemotherapy is another prognostic factor for local recurrence. According to the Birmingham classification suggested by Jeys et al,[11] the five-year local recurrence free survival of 1B tumours (necrosis ≥ 90% and margin ≤ 2 mm) of 91.7% was higher than that of 2A tumours (necrosis < 90% and margin > 2 mm; 84%). Those findings imply that a good response to neoadjuvant chemotherapy should be emphasized over a safe margin in terms of the risk of local recurrence.

In our study, 14 of the 16 patients were good responders, with MRI proving to be effective for assessing the response to neoadjuvant chemotherapy. San-Julian et al[7] reported that the sensitivity and specificity of MRI for delineating the tumoural extension and revealing the relationship between the tumour and the growth plate were 100% and 90.4%, respectively. We classified the location of the tumour according to the relationship between the tumour and the growth plate (Table II). First, we assessed whether the tumour was in contact with the growth plate and then determined whether the contact was total or partial according to San-Julian's classification system.[7] Another element we focused on was the presence of bone marrow oedema in the epiphysis. Serial MRI before and after the neoadjuvant chemotherapy was performed to confirm the change in the extent of the tumours and bone marrow oedema. All 16 patients showed a decreased extent of bone marrow oedema after neoadjuvant chemotherapy. In particular, eight patients (Patients 1 to 4, 7, 8, 11, and 12) whose oedema was visible at the epiphysis on the initial MRI, showed a significant decrease of oedema after chemotherapy (Fig. 3c). These eight patients were classified as good responders to chemotherapy, and the pathological analysis showed a mean necrosis rate of 97.5% (95% to 100%). Among the cohort, there were two patients in whom slight increase in the tumour size resulted in partial contact with the growth plate after neoadjuvant chemotherapy (Patients 10 and 13). However, these changes were accompanied by the progression of core necrosis and disappearance of bone marrow oedema in the epiphysis. After discussion with radiologists and confirmation that the change of tumour was the result of clearer demarcation of tumour periphery rather than increase of the size, we performed TER. Both of these patients were good responders with a 100% necrosis rate. Intriguingly, Patient 14 showed 60% necrosis on postoperative histology, and consecutive MRI confirmed that the tumour was not in contact with the growth plate before or after neoadjuvant chemotherapy and that the size of the tumour did not increase after neoadjuvant chemotherapy. Moreover, no bone marrow oedema was observed in the epiphysis. We performed TER based on those findings, and the patient has remained CDF without local recurrence.

There were some surgery-related complications in our study. The rate of nonunion was 10% (four nonunion/40 osteotomy level), which is similar to that reported by Mnaymneh et al[23] and better than the rate reported by Muscolo et al.[24] All nonunions occurred in the diaphyseal regions, which is also consistent with previous reports. Regarding graft fracture, early studies reported that the prevalence was 9% to 19%[7,25-27] and only one graft fracture occurred in our study. The two revisions were required. For Patient 2 we performed a vascularized fibular graft after confirmation that the patient's growth plate was closed. This enabled us to capitalize on the advantage of graft hypertrophy for filling a large intercalary defect.[28] Patient 7 declined this option and preferred to receive a further allograft.

In conclusion, TER is an effective limb-salvage technique to treat malignant metaphyseal bone tumours in paediatric and young patients with osteosarcoma in the presence of open physes when a good response to chemotherapy with no progression of the tumour to the epiphysis has been confirmed by MRI. According to our results, TER offers safe clinical outcomes and good functional outcomes of the lower limbs and can be considered a viable option for the patients who satisfy the indications.

Take home message

- TER is an effective limb-salvage technique in paediatric and young osteosarcoma patients with open physes.
- A good response to chemotherapy and no progression of the tumour to the epiphysis must be confirmed by MRI.

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