■ ONCOLOGY

Cryoablation-aided joint retention surgery for epiphysis involvement in osteosarcoma compared with endoprosthetic replacement

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Aims

We have previously reported cryoablation-assisted joint-sparing surgery for osteosarcoma with epiphyseal involvement. However, it is not clear whether this is a comparable alternative to conventional joint arthroplasty in terms of oncological and functional outcomes.

Methods

A total of 22 patients who had localized osteosarcoma with epiphyseal involvement around the knee and underwent limb salvage surgery were allocated to joint preservation (JP) group and joint arthroplasty (JA) group. Subjects were followed with radiographs, Musculoskeletal Tumor Society (MSTS) score, and clinical evaluations at one, three, and five years postoperatively.

Results

Patients in both groups (ten in JP and 12 in JA) did not differ in local recurrence ($p \geq 0.999$) and occurrence of metastases ($p \geq 0.999$). Overall survival was similar in both groups ($p = 0.858$). Patients in the JP group had less range of motion (ROM) of the knee ($p < 0.001$) and lower MSTS scores ($p = 0.010$) compared with those of the JA group only at one year postoperatively. There was no difference between groups either at three years for ROM ($p = 0.185$) and MSTS score ($p = 0.678$) or at five years for ROM ($p = 0.687$) and MSTS score ($p = 0.536$), postoperatively. Patients in the JA group tended to have more complications ($p = 0.074$). Survival of primary reconstruction in the JP group was better than that of the JA group ($p = 0.030$).

Conclusion

Cryoablation-aided joint-sparing surgery offers native joint preservation with comparable functional recovery and more durable reconstruction without jeopardizing oncological outcomes compared with conventional limb salvage surgery.

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Introduction

With the advancement in adjuvant chemotherapy and reconstructive procedures, the opportunity may exist for patients with osteosarcoma around the knee to have their affected limb surgically preserved.[1,2] Osteosarcomas with epiphyseal involvement usually necessitate joint resection and prosthetic replacement for tumour control.[3] However, prosthetic reconstruction may be associated with aseptic loosening and mechanical failure, and require subsequent revision surgery.[4,5] There have been attempts to improve contiguous joint function by intercalary resection with retention of the articular portion for osteosarcoma not transgressing the epiphysis.[6-8] Intercalary resection may result in superior joint function by not disturbing the inherent stability and congruence of the joint, and avoidance of long-term endoprosthetic failure.[3,9]

There are reports of attempted retention of the native knee even where the tumour has invaded the epiphysis.[10-12] Tsuchiya et al[13] described "recycling liquid nitrogen ablated tumour bearing bone" in preserving the native joint with acceptable clinical outcomes. We introduced a joint-preserving method in which an argon-based cryoprobe was used to ablate the tumour which had invaded the epiphysis, thus allowing subsequent safe

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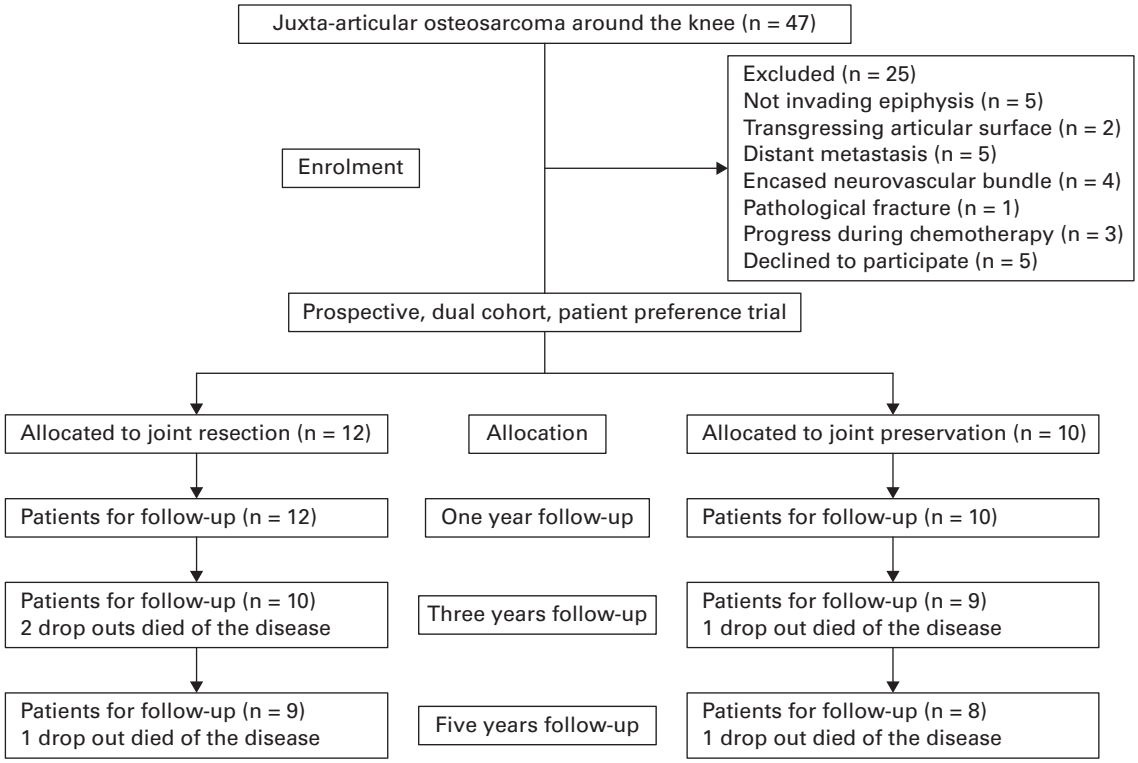

Fig. 1

Flowchart of patient participation in the study.

Table I. Baseline characteristics of the groups.

Characteristic	JP group (n = 10)	JA group (n = 12)	p-value
Mean age, yrs (SD)	14.2 (2.4)	15.3 (2.3)	0.241*
Sex, n (%)			0.415†
Male	3 (30)	6 (50)	
Female	7 (70)	6 (50)	
Anatomical location, n (%)			> 0.999†
Femur	5 (50)	7 (58)	
Tibia	5 (50)	5 (42)	
Mean resection length (SD)	11.8 (2.0)	12.6 (2.3)	0.405*
Soft-tissue margin, n (%)			> 0.999†
Wide	4 (40)	5 (42)	
Marginal	6 (60)	7 (58)	

*Analysis of variance.
†Chi-squared test.
JA, joint arthroplasty; JP, joint preservation; SD, standard deviation.

transepiphyseal osteotomy and joint-sparing intercalary resection.[14] Although acceptable outcomes were previously reported, it is uncertain if these methods match or are superior to traditional intra-articular resection and endoprosthetic reconstruction in terms of tumour control and functional recovery. Only one report has been published in which the local recurrence and the revision rates were compared between joint preservation and resection;[15] however, it was a retrospective study with inherent drawbacks such as lack of strict inclusion criteria or unified treatment protocol.

In this prospective study, we compared oncological and functional outcomes between the patients with cryoablation-assisted joint retention surgery and those with conventional intra-articular resection and endoprosthetic reconstruction. The inclusion criteria were the same in each group so we could assess the clinical outcomes of the two different approaches objectively.

Methods

We conducted a single-centre, prospective, patient preference controlled clinical study that was undertaken in accordance with the Declaration of Helsinki[16] ethical principles for medical research involving human subjects and was approved by our institutional review board.

Patient selection. All patients aged between ten and 20 years who had localized juxta-articular osteosarcoma around the knee-invading epiphysis but not transgressing the articular cartilage were invited to participate in study. All patients were scheduled for limb salvage surgery and underwent neoadjuvant chemotherapy. Enrolment was performed within a week after accomplishment of preoperative chemotherapy from January 2008 to July 2013. We engaged all patients participating in this study in a thorough discussion of risks, benefits, and options of joint arthroplasty (JA group, intra-articular tumour resection, and endoprosthetic reconstruction) and joint preservation (JP group, cryoablation-assisted transepiphyseal intercalary resection, and biological reconstruction) prior to enrolment. For the patients who were willing to undergo joint-sparing surgery, we specifically informed them of the risk of local recurrence, delayed function recovery, necrosis of the epiphysis and subsequent collapse, and loss of the retained epiphysis. Each patient signed a detailed informed consent form. Patients were excluded if they

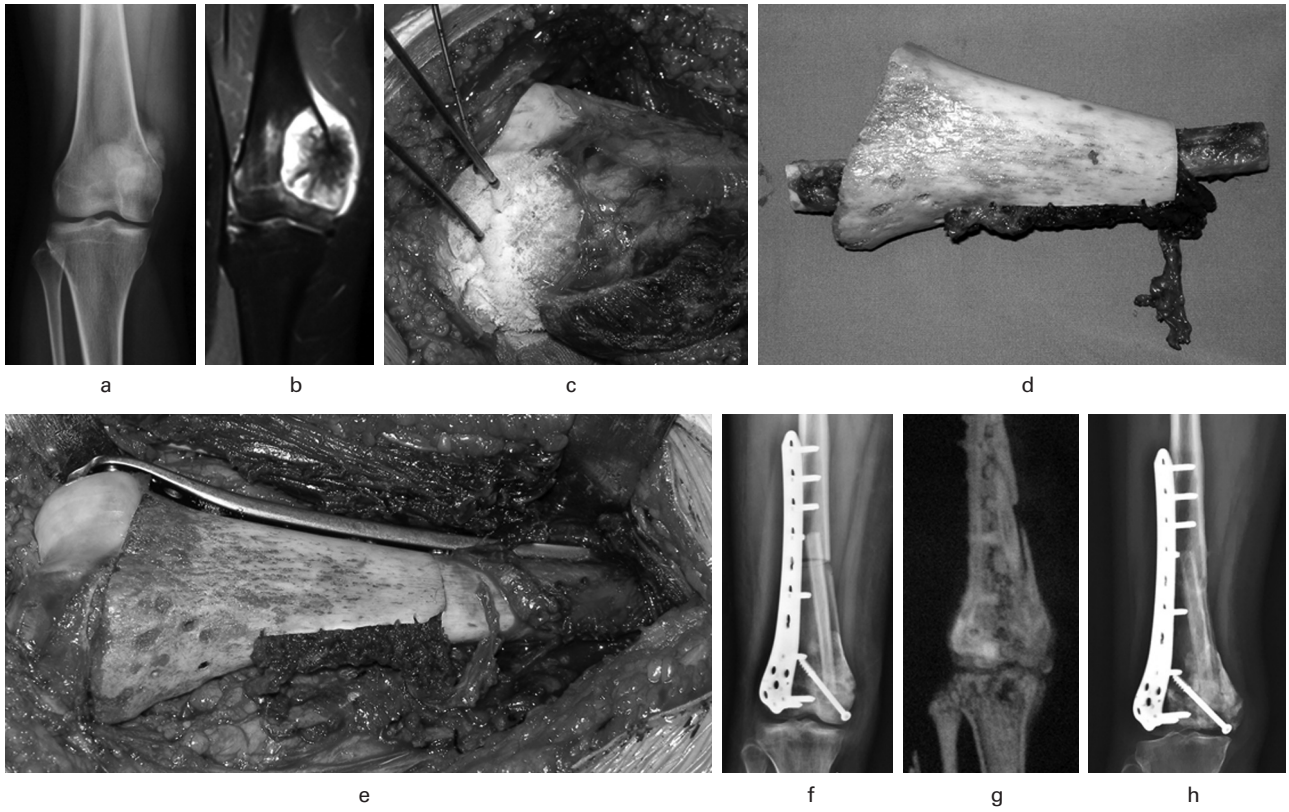

Fig. 2

A 17-year-old female patient had an osteosarcoma of the distal femur. She underwent transepiphyseal resection of an epiphyseal osteosarcoma after adjuvant cryoablation. a) The radiograph reveals an osteosarcoma in the patient's distal femur. b) Her MRI shows the tumour invading the medial condyle of the femur. Intraoperative photographs show c) the argon-based probe ablating the medial condyle. d) The vascularized fibular flap was placed inside the previously liquid nitrogen devitalized tumour-bearing autograft. e) The distal femoral articular surface was preserved and defect was reconstructed. f) Postoperative anteroposterior radiograph shows reconstruction. g) Single photon emission CT scan shows osteonecrosis of the medial condyle and normal viability of the lateral condyle. h) A radiograph obtained five years postoperatively shows mild collapse of the medial condyle.

Table II. Oncological outcomes.

Variable	JP group (n = 10)	JA group (n = 12)	p-value*
Oncological accident, n			
Local recurrence	0	1	1.000
Metastasis	3	3	1.000
Oncological outcome			
CDF	7	9	
NED after treatment of pulmonary metastases	1	Not applicable	
DOD	2	3	

*Chi-squared test.
CDF, continuous disease-free; DOD, died of disease; JA, joint arthroplasty; JP, joint preservation; NED, no evidence of disease.

had multiple lesions; had distant metastasis; had a pathological fracture; had major neurovascular bundle encapsulation; or had poor chemotherapy response (obvious tumour enlargement on MRIs during neoadjuvant chemotherapy).

Patient characteristics. The flow of participants through the trial is shown in Figure 1. A total of 47 patients who had juxta-articular osteosarcoma around the knee were screened over 65 months, and 25 patients were excluded: of these, 20 for not meeting inclusion criteria and five because of not wishing to participate. Follow-up was complete for all patients. The age, sex distribution, tumour location, resection length, and soft-tissue surgical margin were nearly identical in the two groups (Table I).

Surgical procedure. The surgery was performed by two experienced oncological surgeons (JL, ZW) using a standardized procedure consisting of the following basic steps which have been reported previously.[17] After wide exposure, tumour resectability was determined by exploration of the popliteal space and vessels. The major vascular bundle (superficial femoral, popliteal vessels), sciatic nerve, and healthy soft tissue was separated from tumour. The pedunculated tumour-bearing knee joint was mobilized following proximal femoral or distal tibial one-site osteotomy, 2 cm beyond the tumour, as determined by preoperative MRI. In the JA group, the tumour was resected after disarticulating the joint and endoprosthetic reconstruction was performed with the use of an endoprosthetic system. In the JP group, after three cycles of in situ argon-based cryoablation applied to ablate the epiphyseal tumour, intercalary tumour resection was accomplished following transepiphyseal osteotomy with preservation of at least 1 cm of the bone adjacent to the

Table III. Musculoskeletal Tumor Society (MSTS) scores and range of motion (ROM) of the knee reported by year.

Year	Mean MSTS score (SD)		p-value*†	Mean ROM, % of contralateral side (SD)		p-value*†
	JP	JA		JP	JA	
1	21.88 (1.25)	23.89 (1.54)	0.010	63.25 (5.75)	76.33 (4.74)	< 0.001
3	23.88 (0.99)	24.11 (1.27)	0.678	73.88 (5.55)	77.22 (4.49)	0.185
5	24.75 (1.39)	24.33 (1.32)	0.536	74.88 (3.68)	75.89 (6.03)	0.687
p-value*‡	0.011	> 0.999		0.001	> 0.999	
p-value*§	< 0.001	> 0.999		< 0.001	> 0.999	
p-value*¶	0.498	> 0.999		> 0.999	> 0.999	

*Analysis of variance.
†Difference between treatment groups.
‡1 vs 3.
§1 vs 5.
¶3 vs 5.
JA, joint arthroplasty; JP, joint preservation; SD, standard deviation.

joint line; then Capanna reconstructive technique[18] (massive allografts or extracorporeal liquid nitrogen devitalized tumour bearing bone, combined with vascularized fibula graft) was employed for the intercalary reconstruction. The medial gastrocnemius muscle was used for a soft-to-soft tissue reconstruction of the extensor mechanism as well as coverage of the prosthesis or allograft in the proximal tibial reconstruction. A clinical example is shown in Figure 2.

Clinical outcomes. All patients were followed up at one month, three months, every three months for two years, every six months until three years, and annually thereafter. Screening for local recurrence was conducted according to symptomatology, plain radiological appearance, or bone scan findings. The presence of metastases was determined by routine chest CT and bone scan. Functional evaluation was performed using the system suggested by the Musculoskeletal Tumor Society (MSTS).[19] The MSTS score measured six parameters: pain, function, emotional acceptance, use of walking supports, walking ability, and gait. Each parameter is given a value from 0 to 5. The individual scores are added together to obtain final score, with a maximum of 30 points being defined as normal function. The range of motion (ROM) of the knee was examined and recorded as percentage of the contralateral side. MSTS score and ROM of the knee were recorded at the one-, three-, and five-year follow-ups.

SPECT-CT was used to assess viability and osteonecrosis of the remaining epiphysis at one week and three months postoperatively. We obtained radiographs to evaluate bone union, allograft fracture, degenerative changes of the knee, breakage of implants, and prosthetic aseptic loosening. Major complications were defined as those necessitating additional surgery.

Statistical analysis. The MSTS score, the primary outcome measure, was used to perform an a priori power analysis. We considered an increase of 2.5 points to be the minimal clinically important difference on the basis of preliminary data indicating a mean score of 24. A power analysis with two-sided hypothesis testing and $\alpha = 0.05$ indicated that ten patients in each group were needed in order to identify the minimal clinically important difference of 2.5 points with 80% power. Continuous variables are presented as the mean and standard deviation (SD). The differences between JP and JA groups in MSTS score and change in knee ROM over time were analyzed with a repeated-measures analysis of variance (ANOVA). Nonparametric chi-squared tests were used to compare local recurrence, the development of metastases, and major complications between the two groups. Overall and primary reconstruction survival rates were estimated with use of the Kaplan-Meier method. Primary reconstruction survival curves was defined as the time from date of index surgery to the time of removal of the primary reconstruction for any reason. We generated Kaplan-Meier survivorship curves between the two groups and compared them with log rank testing. Significance was set at a p-value < 0.05 (two-sided). All analyses were performed useing IBM SPSS v.25.0 software (IBM, USA).

Results

Oncological outcomes. In the JP group, no local recurrence occurred. Three patients developed pulmonary metastases; two died of the disease at 16 and 23 months postoperatively. One patient underwent pulmonary lobectomy and had no evidence of disease at five years' follow-up. In the JA group, one patient who had local recurrence around the posterior tibial vessels underwent amputation and died of subsequent pulmonary metastases 13 months after discovery of the local recurrence. Three patients who had pulmonary metastases all died of the disease. With the numbers available, we found no differences between the two groups in terms of local recurrence and metastases (Table II). Survivorship with the end point being date of death was similar in both groups with survival of the JA group versus the JP group being 75% (95% confidence interval (CI) 50.5% to 99.5%) vs 80% (95% CI 55.31% to 100%)) at five years (p = 0.858, log rank test; Figure 3).

Functional results. The overall MSTS scores for our study patients ranged from 20 to 28. Differences in the MSTS scores between the JP and the JA groups was significant at one year but not at three and five years postoperatively. MSTS score analysis revealed significant improvement from one year to three years in the JP groups; in contrast, MSTS scores were similar at all follow-up periods in the JA groups (Table III).

ROM of knee of the JA group was significantly better than that of the JP group at first year postoperatively. No significant difference was found between the two groups at three and five years postoperatively. An analysis of ROM of knee did not reveal significant differences among the JA group during any follow-up period. The JP group showed significant

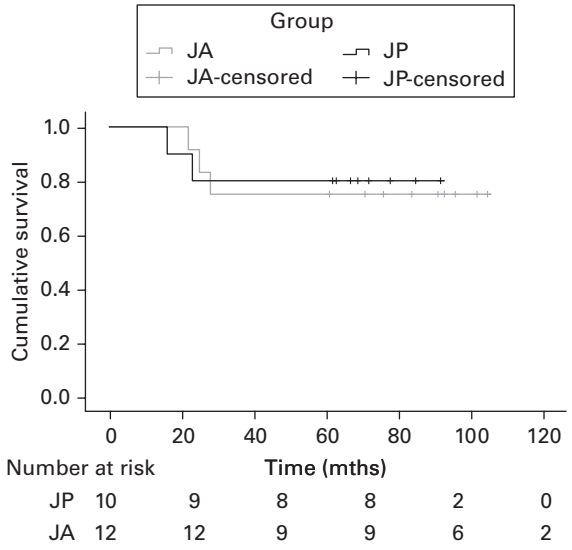

Fig. 3

Kaplan-Meier overall survivorship showing survival of the joint preservation (JP) group versus joint arthroplasty (JA) group being 75% versus 80% at five years.

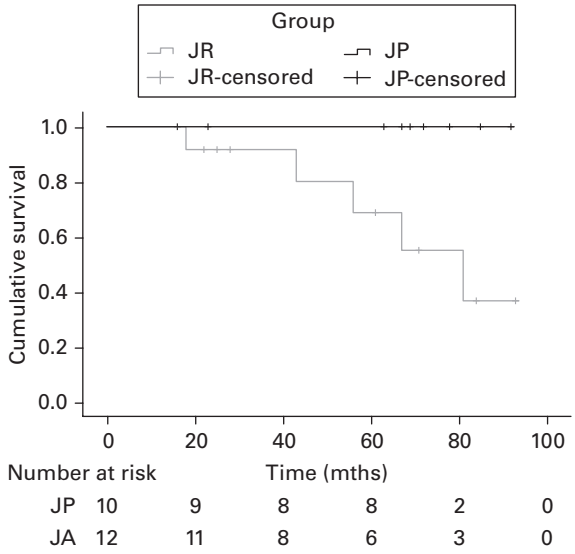

Fig. 4

Kaplan-Meier survivorship showing high survival of the primary reconstruction using revision as the end point for the joint preservation (JP) group versus joint arthroplasty (JA) group being 100% versus 68.2% at five years.

gains in ROM from the first year to the third year postoperatively (Table III).

Primary reconstruction survival and major complications. All patients in the JP group had their saved epiphysis and primary reconstruction intact. No additional surgical procedure was performed to treat orthopaedic complications. In seven patients the preserved epiphysis revealed no metabolic activity and three revealed partial metabolic activities ion bone scanning. Osteonecrosis of the residual epiphysis was seen in all patients. All patients, except one, revealed degenerative changes of the knee in the JP group. Limb-length discrepancy ranging from 1 cm to 2.5 cm was observed in four patients and no patient underwent surgical treatment for this. In contrast, four of the 12 patients in the JA group lost their primary endoprosthesis owing to amputation, breakage, loosening, and infection, respectively. Five patients had limb-length discrepancy ranging from 1 cm to 2 cm. The difference in Kaplan-Meier survivorship was significant ($p = 0.030$, log rank test) when comparing survival of the surgical reconstruction using revision as an end point for the JP group versus the JA group, which was 100% versus 68.2% (95% CI 37.92% to 98.28%) at five years (Figure 4).

In the JP group, a pulmonary lobectomy was performed for metatstatic disease in one patient. Nine of the ten patients achieved healing without major complications. Of the 12 patients in the JA group, secondary surgery was performed in six, one for an oncological reason and five for orthopaedic problems. Patients in the JA group tended to have more major complications (6/12 vs 1/10; $p = 0.074$, chi-squared test).

Discussion

Local recurrence in osteosarcoma following limb-preserving surgery is associated with an ominous prognosis. The pathological response to chemotherapy, type of surgical margin, and the proximity of osteosarcoma to major blood vessels are fundamental issues that affect local recurrence.[20–22] In this study, an ablative margin was achieved in the JP group and wide margin was achieved in the JA group. No significant difference was found in local relapse in both groups, which suggested intralesional resection through cryoablation bone is comparable to wide resection in terms of its influence on local relapse. Distant metastasis and overall patient survival were also similar in both groups. These comparative outcomes suggested that cryoablation-assisted joint retention surgery is not detrimental to local and systemic tumour control when compared with classic joint-sacrificed limb-sparing surgery.

There were two limitations to this study. The first limitation was introducing the concept of an ablative margin. In an attempt to preserve the epiphysis, we had to perform intercalary resection through in situ cryoablation at the epiphysis. Historically, there was no term to describe this type of resection.[23,24] Although pathological examination of specimens revealed dead tumour cell at the osteotomy site, no histological evidence was obtained to support the thoroughly ablative value of eradicating tumours in the residual epiphysis. Therefore, the concept of ablative margin is exploratory in nature and we hope more studies will focus on its effectiveness in future. Second, histological response to preoperative chemotherapy remains a powerful prognostic factor for local recurrence in addition to type of surgical margin.[4,20] We sought to unify chemotherapy response in both groups by excluding patients who had a poor histological response to neoadjuvant chemotherapy. However, tumour necrosis rate, used for evaluation of chemotherapy response, is generally obtained after surgery and not available in this study. We accept that using clinical and radiological findings rather than histological assessment for chemotherapy evaluation is a weakness of this study.

There is a paucity of literature regarding the approach of retaining the native joint when tumour invades epiphysis. In an attempt to save the native knee in this situation, Tsuchiya et al[13] reported an approach, which includes making a single osteotomy, immersing the tumour-bearing bone along with its attached joint into liquid nitrogen to sterilize tumour-bearing bone, and reconstruction with sterilized tumour-bearing bone.[13] Different from the Tsuchiya technique, we used argon-based cryoprobe to ablate epiphyseal tumour and produce a zone of ''necrotic tumour-bearing bone'', allowing for subsequent intra-epiphyseal osteotomy and native joint end preservation. This precise ablation is intended to spare the epiphysis as well as preserve partial viability of a healthy epiphysis and the cruciate ligaments. Three of the ten remaining epiphyses were viable in varying degrees which was verified by early postoperative bone scan. Theoretically, the cruciate ligament not only offers proprioception and stability of the knee and but also facilitates revascularization of retained epiphysis. Given that the MSTS score and ROM of knee were similar in both groups at five years' follow-up, we believe this approach expands the indication for joint salvage procedures and is an acceptable alternative to joint resection in the limb salvage surgery.

It may be proposed that as ablation is so effective, perhaps the entire tumour could be ablated, thereby avoiding any resection. However, ablated tumour-bearing bone has poor biomechanical characteristics that have been reported to lead to complications such as nonunion and fracture.[25–28] The combination of a vascularized fibula with allograft or extracorporeal ablated autograft has the advantage of quality bone mass restoration with a low incidence of complications.[18,28] Vascularized fibula is a strut supporting the residual epiphysis mechanically, as well as attempting to facilitate revitalization of the epiphysis, but it is acknowledged that this did not appear to occur in our patients; furthermore, it promotes healing between allograft and residual bone by providing osteoblastic tissue. No fracture or nonunion occurred in the JP group, indicating it is an effective and durable reconstruction. All reconstructions in the JP group were intact at a minimum of five years' follow-up. In contrast, four of 12 patients in the JA group had their original endoprosthesis revised due to orthopaedic complications, which is similar to previously reported results.[5,29] There was significantly better survivorship of primary reconstruction and a trend towards a low rate of major complications in the JP group. This impressive outcome suggests that biological reconstruction is more durable than endoprosthetic reconstruction at the mid-term follow-up.

Despite its merits, some weakness of the joint preservation technique should not be ignored. First, full weightbearing in the JP group was not allowed until bone integration was obvious radiologically. Therefore, patients in the JP group have prolonged non-weightbearing time compared to that of the patients in the JA group. Second, all patients in the JP group developed osteoarthritis (OA), revealing osteophyte formation and reduction in the joint space. We surmised that osteonecrosis leading to the microcollapse of subchondral bone during weightbearing and joint instability may cause degeneration of the knee. Although degenerative changes did not preclude favourable functional outcome at mid-term follow-up, we anticipate that OA will become more severe in the long term, and revision surgery will be inevitable in some patients. Third, the patients in the JP group had a lower MSTS score and poorer ROM of the knee compared with that in the JA group at the first-year follow-up; however, our data did show a trend toward higher MSTS scores and improved ROM of the knee with increasing follow-up, which reflected the gradual biological healing process in the JP group.

In conclusion, intercalary resection through cryoablated tumour bearing bone allows retention of native joint for juxta-articular osteosarcoma with epiphyseal extension. This surgical strategy provides an alternative to conventional intra-articular tumour resection and endoprosthetic reconstruction, with similar oncological outcomes, comparable functional outcomes, and fewer major complications. Further research should focus on identifying appropriate indications for cryosurgery, with sterilization of the tumour in a precise manner while preserving as much viability of healthy epiphysis as possible.

Take home message

- Cryoablation-aided joint-sparing surgery offers native joint preservation with comparable functional recovery and more durable reconstruction without jeopardizing oncological outcomes compared with conventional limb salvage surgery.

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J. Li: Performed the surgery, Collected and analyzed the data, Drafted the manuscript.
Y. Lu: Collected and analyzed the data, Assessed the clinical and imaging outcomes.
G. Chen: Collected and analyzed the data, Assessed the clinical and imaging outcomes.
M. Li: Performed the surgery, Assessed the clinical and imaging outcomes.
X. Xiao: Performed the surgery, Assessed the clinical and imaging outcomes.
C. Ji: Performed the surgery, Assessed the clinical and imaging outcomes.
Z. Wang: Performed the surgery, Conceptualized and designed the study, Revised the manuscript.
Z. Guo: Conceptualized and designed the study, Revised the manuscript.

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Ethical review statement:
This study has been performed in accordance with the Helsinki Declaration and approved by the Clinical Research Ethics Committee of Xi Jing Hospital.

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