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Joint-preservation surgery for pediatric osteosarcoma of the knee joint

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Abstract
The multi-disciplinary approach involving imaging, multi-agent chemotherapy, meticulous surgical procedures, and careful postoperative care has facilitated an increase in the use of limb-sparing surgery for pediatric osteosarcoma. Osteosarcoma usually occurs around the metaphysis of the distal femur or proximal tibia and needs wide excision with the adjacent joint and replacement by a megaprosthesis. The recent advancement in imaging modalities and surgical techniques supports joint-preservation surgery (JPS), involving the preservation of the adjacent epiphysis, for select patients following careful assessment of the tumor margins and precise tumor excision. An advantage of this surgery is that it maintains the adjacent joint and preserves the growth of the residual epiphysis, which provides excellent limb function. Various reconstruction options are available, including allograft, tumor-devitalized autograft, vascularized fibula graft, distraction osteogenesis, and custom-made implants. However, several complications are inevitable with these options, such as loosening, non-union at the host-graft junction, infection, fracture, implant loosening, breakage, deformity, limb-length discrepancy related to the reconstruction methods, or patient growth in pediatric osteosarcoma. Surgeons should fully understand the advantages and disadvantages of this procedure. In this review, we discuss the concept of JPS, types of reconstruction methods, and current treatment outcomes. It is our opinion that the further analysis by multi-institutional setting is necessary to clarify long-term outcomes and establish global guidelines on the indications and surgical procedure for JPS.

Keywords Pediatric osteosarcoma · Joint-preservation surgery · Biological reconstruction · Knee joint

1 Introduction

The multi-disciplinary approach combining advanced imaging modalities, multi-agent chemotherapy, and meticulous surgical procedures has established the consensus of performing limb-sparing surgery in the treatment of osteosarcoma, which is the most common pediatric malignant bone tumor [1]. Previous studies have reported that survival following a limb-sparing surgery was equivalent to that following surgical amputation. However, the most important aspect of surgery is to completely remove the tumor with safe margins. Local recurrence has been reported as one of the prognostic factors [1, 2]. Osteosarcoma usually develops in metaphyseal locations around the knee and usually requires excision with the adjacent joint [3].

Prosthetic replacement is the most common method utilized in knee osteosarcoma (Fig. 1a–g) to reconstruct the large bony defect. Advantages of this procedure include the technical simplicity, the immediate postoperative recovery of mechanical stability, and early functional recovery. Its short- to mid-term outcomes are satisfactory. However, the incidence of long-term complications such as infection, loosening, breakage, and bushing wear that require revision surgery remains high [4, 5]. An osteoarticular allograft is one of the options available to resolve these complications. However, joint instability and incongruity remain major problems with this technique as well [6]. Moreover, resection of the growth plate causes limb-length discrepancy (LLD), which is one of the major complications following surgery. To resolve this problem, an expandable prosthesis has been developed (Fig. 1f) which has an invasive or non-invasive mechanism. In the minimally invasive system, the prosthesis contains an

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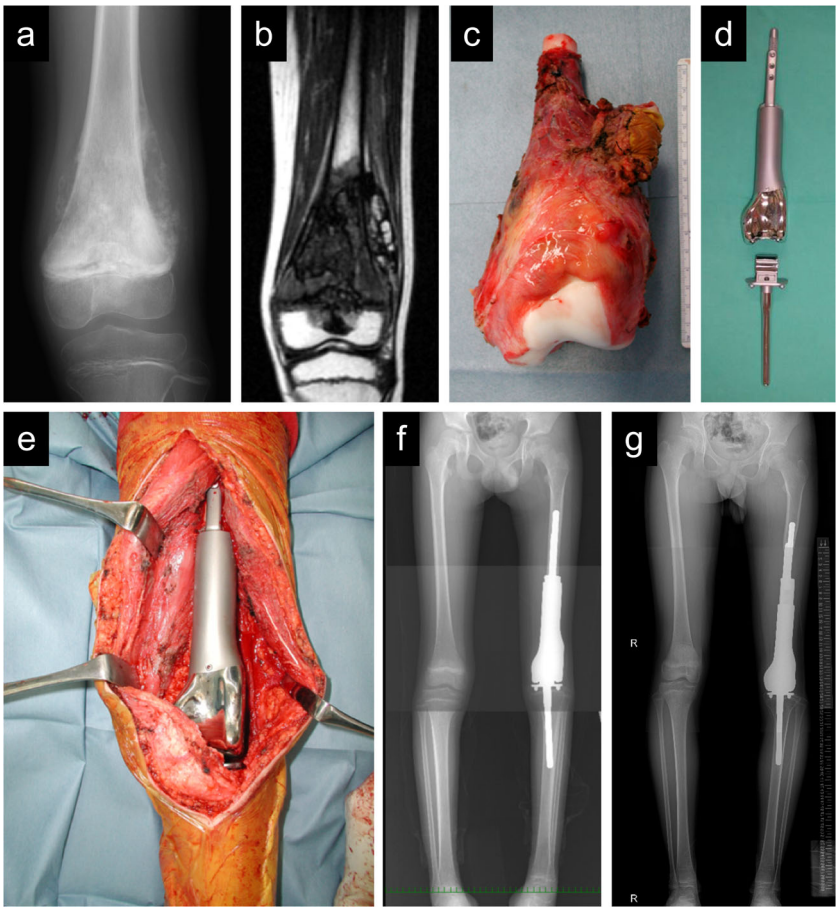

Fig. 1 An 11-year-old boy with osteosarcoma of the left distal femur. Preoperative plain radiograph (**a**) and T1-weighted magnetic resonance image (**b**). The resected specimen (**c**). An expandable knee prosthesis (**d**). A photograph after excision of diseased bone and replacement by expandable knee prosthesis (**e**). Plain radiographs immediately after surgery (**f**) and 38 months after surgery (**g**), the latter with 60-mm elongation of the prosthetic

elongating screw that is rotated *via* a small incision. However, there are concerns that the elongation procedure needs to be performed in the operating room and under general anesthesia [7]. By contrast, the non-invasive prosthesis has a stem that can be elongated by rotating either an external magnet or an electromagnetic field. This elongating mechanism can reduce risks related to an invasive procedure [8]. However, the complication rate, mainly due to mechanical failure, remains high [9, 10].

Modern technology, such as advanced imaging [11], precise tumor excision with close tumor margin under guidance of an image intensifier or a navigation system [12], and rigid fixation technique with a locking plate [13], has established joint-preservation surgery (JPS) as the standard treatment for patients responsive to neoadjuvant chemotherapy and without tumor invasion of the epiphysis [14]. JPS enables preservation of the adjacent joint, which is crucial for achieving excellent postoperative limb function. As stable and durable intercalary reconstruction of the bony defect is necessary, biological methods of reconstruction, including allograft [14], tumor-devitalized autograft [15], vascularized fibular graft [16], and distraction osteogenesis (DO) [17], and non-biological methods with custom-made implants [12] have been developed. In tumor-devitalized autograft, the resected tumor-bearing autograft is recycled after devitalization by heat treatment [18], freezing by liquid nitrogen [15], or irradiation [19]. Here we discuss the concept of JPS, types of reconstruction methods, current treatment outcomes, and associated benefits and complications.

1.1 Joint-preserving surgery

JPS is an alternative procedure of excising the tumor that spares the epiphysis and preserves adjacent joints and ligaments [20]. This procedure is expected to provide excellent limb function. JPS is composed of precise tumor excision, augmentation of the defect using biological materials or prosthetic implant, and rigid fixation of the residual epiphysis using supplemental material and host bone. This procedure is indicated to cases that meet the following criteria: (1) favorable radiological responses to neoadjuvant chemotherapy, described as findings of massive sclerotic changes or well-marginated tumor on plain radiographs, marked shrinkage of extraosseous tumors on magnetic resonance imaging (MRI), disappearance of tumor stains on angiograms, or complete disappearance of accumulation in the tumor on TI ^{201} scintigrams [21]; (2) residual epiphysis thickness > 1 cm; (3) surgical margin is possible with ≥ 10 mm; and (4) either no

apparent distant metastasis (Enneking stages IIA and IIB) or resectable distant metastasis (Enneking stage III) [22].

The authors of this review also categorized tumor excision into 3 types: transmetaphyseal excision (preservation of the epiphyseal plate), transphyseal excision (partial removal of the epiphyseal plate), and transepiphyseal excision (total removal of the epiphyseal plate) (Fig. 2) [23]. Transphyseal and transepiphyseal excisions are indicated in cases in which the tumor does not extend to the epiphysis, as judged by T1-weighted MRI and short tau inversion recovery (STIR) images [11]. Transepiphyseal excision is the most complicated osteotomy because of the small residual epiphysis.

A previous retrospective study reviewed 12 osteosarcoma patients who underwent JPS (8 cases involving the distal femur and 4 cases involving the proximal tibia). In this study, close marginal tumor excision was carefully performed using a microsurgical saw following the insertion of a K-wire into the osteotomy line under fluoroscopy [23]. Wong et al. reported that a navigation-guided surgery helps in accurate excision [12]. In the 8 cases studied, the osteotomy line was accurately placed with a difference of 2 mm or less in any dimension. They noted no local recurrence at the longest follow-up (mean = 41 months postsurgery). The mean Musculoskeletal Tumor Society (MSTS) score [24] was 29 (range = 28–30). No complications related to the navigation-guided surgery and intraoperative complications were noted. Moreover, there was no failure of fixation at the residual epiphysis.

Recently, a patient-specific guide has been developed. Bellanova et al. reported 4 cases treated using surgical guides (i.e., patient-specific instruments) for pediatric tibial bone sarcoma resection. They successfully resected all tumors with histologically negative margins [25]. However, there is still a concern regarding the long-term safety of close surgical margin resection for JPS and whether tumor extension to the epiphysis could be accurately evaluated. Hoffer et al. reported that epiphyseal extension of osteosarcoma could be successfully confirmed on MRI as a dark signal on T1 images and a bright signal on STIR images [11]. Based on these findings, JPS was determined to lead to better postoperative joint mobility [16]. In another study, Andreou et al. resected 123 of 1355 osteosarcoma cases with the close surgical margin, and they concluded that the close margins did not contribute to the increased risk of local recurrence [26]. Several reconstruction methods have been developed to fill the large bony defects following tumor excision. Two main reconstruction methods are categorized into biological methods, including allograft [14], tumor-devitalized autograft [15], vascularized fibular graft [16], and DO [17] and non-biological methods, using custom-made implants [12].

1.2 Allograft

Allografts enable incorporation of the host-to-allograft junction and the restoration of bone stock, which could facilitate future revision surgery [27]. Allografts also enable reattachment of a ligament or tendon to the graft, which is essential to improving joint stability [28]. However, their reported disadvantages include impaired growth, graft resorption, nonunion, pathological fractures, and high infection rates [29].

Table 1 summarizes the different JPS reconstruction methods and subsequent outcomes including survival, tumor recurrence, and graft survival. Bus et al. reviewed 87 cases of intercalary allograft reconstruction for primary bone tumors. In their study, the incidence of graft failure was 17%, which consisted of graft-related (infection, fracture, and non-union) or unrelated (local recurrence) complications. Moreover,

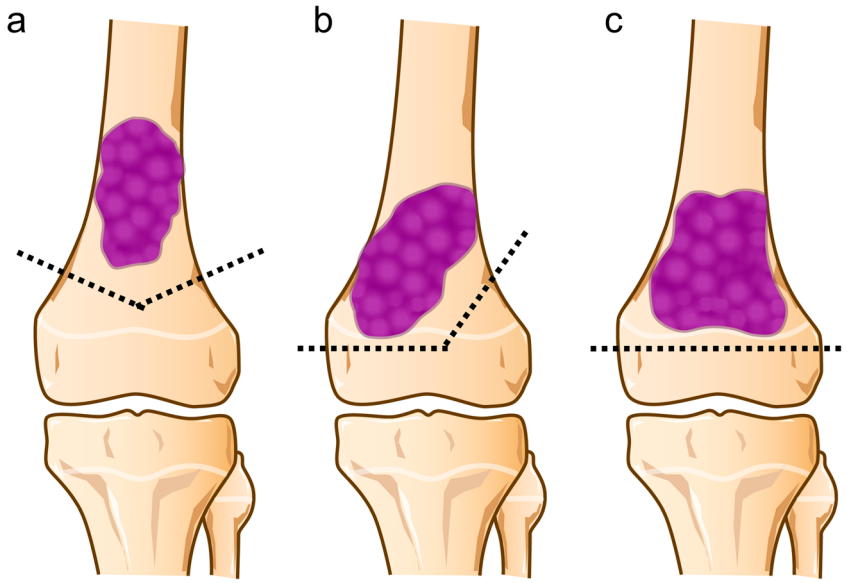

Fig. 2 Diagram showing the classification of tumor excision to preserve the epiphysis. **a** Transmetaphyseal excision (epiphyseal plate preserved), **b** transphyseal excision (partial removal of the epiphyseal plate), and **c** transepiphyseal excision (total removal of the epiphyseal plate). The dotted line indicates the osteotomy line

Table 1 Outcome of JPS in each reconstruction method

Study	Reconstruction	No. of patients (pediatrics)	Histology	Mean age (range)	Follow-up (months)	Graft survival	Recurrence (%)	Complications	MSTS score
Bus MPA [30]	Allograft	78 (41)	OS (34), others (45)	17 (1.5–77.5)	84	68 (87%)	2 (2.3)	Fracture (23), non-union (29), infection (8)	N/A
Muscolo L [31]	Allograft	13 (10)	OS (13)	18 (9–40)	63	12 (92%)	1 (7.7)	Fracture (2), non-union (2), infection (1)	90%
Aponte TL [14]	Allograft	35 (27)	OS (35)	17 (2–50	9 years	26 (74%)	3 (8.6)	Fracture (11), non-union (3), infection (2)	86.7
Houdek MT [32]	Allograft + FVFG	18	OS (9), others (9)	11 (5–18)	8 years	17 (94%)	1 (5.6)	Fracture (3), non-union (6), wound complication (6), LLD (4), deformity (6)	93%
Puri A [33]	ECI	70 (N/A)	OS (38), others (32)	17 (1–36)	56	79% (5 years)	7 (10%)	Non-union (33%), infection (11%), fracture (6%)	N/A
Hong AH [34]	ECI	101 (61)	OS (37), others (64)	23 (3–70)	53	N/A	5 (5%)	Mechanical reason or delayed osteomyelitis (36)	N/A
Sharma DN [35]	ECI	14 (12)	OS (9), Ewing (5)	14 (7–20)	22	100%	3 (13.6%)	Wound infection (2)	88.00%
Wu PK [36]	ECI	79 (N/A)	OS (79)	19 (9–29)	82	84%	12 (15%)	Wound complication (6), non-union (8), fracture (2), implant failure (1), infection (6)	N/A
Manabe J [18]	Pasteurized	25 (13)	OS (12), others (15)	24 (7–77)	52	76%	0	Fracture (3), non-union (5), infection (5)	86%
Jeon DG [37]	Pasteurized	21 (5)	OS (7), others (14)	34.6 (11–59)	74	74% (10 years)	2 (9.5%)	Fracture (2), non-union (5), infection (3)	88%
Qu H [38]	Pasteurized	27 (N/A)	OS (14), others (13)	28.3 (9–73)	62.8	81.5%	2 (7.4%)	Fracture (1), non-union (4), infection (3), fixation failure (4)	93%
Ikuta K [39]	70 °C 15 min + FVFG	24 (16)	OS (21), others (3)	22 (5–61)	88	70.1% (10 years)	3 (12.5%)	Fracture (1), non-union (14), Infection (3), bone absorption(5)	76%
Igarashi K [40]	Frozen	36 (10)	OS (19), others (17)	39 (10–72)	101	29 (80.6%)	4 (11.1%)	Fracture (7), non-union (4), infection (4), fixation failure (4)	Excellent (26), good (7), fair (3)
Wu PK [36]	Frozen	85 (N/A)	OS (85)	20 (8–32)	70	84%	9 (11%)	Wound complication (3), non-union (11), fracture (5), implant failure (2), infection (4)	N/A
Shimozaki S [41]	Frozen	20(9)	OS (11), others (9)	36 (11–79)	56	80%	0	Fracture (3), infection (3), joint destruction (3: osteoarticular graft)	Excellent (18), good (2)
Takeuchi A [23]	Frozen	12	OS (12)	11 (6–14)	63	83.8%	1 (8.3%)	Fracture (4), infection (1), LLD > 30 mm (2)	27.7
Eward WC [42]	FVFG	30 (12)	OS (14), others (16)	29 (7–75)	4.9 years	96.7%	2 (6%)	Fracture (6), non-union (7), infection (3)	N/A
Kiss S [16]	FVFG + ipsilateral fibula	5	OS (2), Ewing (3)	11.2 (5–14)	4.9 years	100%	0	Fracture (3), non-union (1), infection (1)	N/A
Petersen MM [43]	FVFG	8 (6)	OS (4), others (7)	13.6 (4–24)	50	87.5%	0	Fracture (4), non-union (1), infection (1), hip dislocation (1), pseudoarthrosis (1)	22.4
Tsuchiya H [17]	DO	11 (6)	OS (11)	21.5 (9–43)	53.8	100%	0	Pes equinus (1), fracture (1), infection (2), peroneal nerve palsy (1), delayed healing (1)	97.8%

Table 1 (continued)

Study	Reconstruction	No. of patients (pediatrics)	Histology	Mean age (range)	Follow-up (months)	Graft survival	Recurrence (%)	Complications	MSTS score
Demiralp B [44]	DO	13 (6)	OS (7), others (6)	19.6 (7–42)	157	100%	0	Pin tract infection (8), reduced range of motion (5), LLD (2), non-union (3), delayed consolidation (3)	89.5%
Watanabe K [45]	DO	22 (7)	OS (12), others (10)	25.3 (4–71)	202	100%	1 (4.5%)	Fracture (2), non-union (5), delayed consolidation (4), pin tract infection (1)	91.5%
Gupta A [46]	Custom-made implant	8 (5)	OS (6), CS (2)	17.3 (14–21)	24	87.5% (implant)	0	Septicemia (1), joint contracture (1)	24
Spiegelberg BGI [47]	Custom-made implant	8 (N/A)	OS (5), others (3)	28.9 (8–43)	35	75% (implant)	1 (12.5%)	Fracture (1)	79%
Agarwal M [48]	Custom-made implant	6 (5)	OS (3), Ewing (3)	14.5 (range, 8–43)	34	100% (implant)	0	Reduced range of motion (1)	28.4%
Wong KC [12]	Custom-made implant	6 (4)	OS (6)	17 (6–46)	41	83.3% (implant)	0	Aseptic loosening (1)	29.1%

FVFG free vascularized fibular graft, *DO* distraction osteogenesis, *N/A* not available, *OS* osteosarcoma, *LLD* limb-length discrepancy, MSTS (excellent 75–100%, good 70–74%, moderate 60–69%, fair 50–59%, poor < 50%)

patients aged > 18 years with graft lengths > 15 cm are associated with significantly increased risk of graft failure and are recommended to undergo bridging osteosynthesis using plate fixation [30]. Furthermore, Muscolo et al. reported 30 cases of allograft reconstruction following a transepiphyseal osteotomy in patients with high-grade metaphyseal osteosarcoma of the knee. They described only one graft-unrelated complication of a soft tissue recurrence with no recurrence in the residual epiphysis [31]. In addition, Aponte-Tinao et al. reviewed a large series (35 cases including 12 pediatric patients) with a longer follow-up period, of the same reconstruction for metaphyseal osteosarcoma of the knee. Although a second surgical procedure was needed in 19 patients (54.3%) due to 16 graft-related complications (11 fractures, 3 diaphyseal non-unions, 2 deep infections) and 3 graft-unrelated complications (3 local recurrences), the mean MSTS score was 26, and no recurrence was observed in the residual epiphyses. The residual epiphysis was eventually removed in 5 patients (14.3%) due to fractures ($n = 3$), amputation ($n = 1$), and infection ($n = 1$) [14]. Grafting combined with vascularized fibula, called Capanna's technique, has been reported useful in reducing the risk of complications [49].

Houdek et al. reported 18 pediatric patients who underwent Capanna's reconstruction technique for lower extremity limb salvage. Fourteen patients needed additional surgery to treat non-union ($n = 6$), wound complications ($n = 5$), and graft fracture ($n = 3$). Four patients underwent the limb-lengthening procedure, and 6 patients underwent deformity correction. Seventeen of the patients (94%) achieved good MSTS scores of 93%, and the overall limb salvage rate was 94%. They concluded that combining intramedullary vascularized free fibulas for large allografts might be a reliable method in the lower extremity. They proposed that younger patients are good candidates for this procedure, given their high risks of allograft fracture and infection. Despite the high risk of reoperation, this technique is worth considering because of its favorable limb function and oncological outcomes [32].

1.3 Tumor-devitalized autograft

Tumor-devitalized autograft is a unique biological reconstruction method that involves re-implantation of tumor-bearing bone after devitalized treatment (extracorporeal irradiation [19], heat treatment [18], and freezing [15]). Its advantages are as follows: perfect fit to the defect, no risk of viral transmission and immune response problems, easy attachment of muscles and tendons, preservation of bone stock, biological stability after graft union, and absence of donor site morbidity [15]. However, various complications such as infection, fracture, non-union, and implant breakage were reported [50].

1.3.1 Extracorporeal irradiated bone

Extracorporeal irradiated bone (ECI) autograft was first described by Spira et al. in 1968 [51]. In this method, the resected tumor bone is irradiated with a dose of 50 to 300 Gy [52]. In a previous study, Uyttendaele et al. reported the outcomes of 17 cases with ECI reconstruction, and complications were identified in 10 cases (infection, false joint, bone resorption, osteonecrosis, recurrence, and dislocation). However, they stated that ECI was an alternative to prosthesis and bone allografts [19]. Moreover, Puri et al. reviewed 70 patients (mean age of 17 years) who underwent ECI autograft with a mean follow-up term of 61 months. Complications include non-union (33%), infection (11%), fracture (6%), and recurrence from soft tissue (10%). They moreover found that metaphyseal osteotomies had a higher graft-host junction union rate (91%) without additional procedures than diaphyseal osteotomies (71%). The 5-year graft survival was 79%. Placement of a small plate at the site of diaphyseal osteotomy was the key to reduce non-union [33].

Hong et al. reported the clinical outcome of 101 cases including 62 pediatric patients, with a median follow-up of 53 months. Despite 5 local recurrences (1 Ewing sarcoma and 4 chondrosarcomas), limb preservation was achieved in 97 patients. The 5-year cumulative overall survival was 81.9% in Ewing sarcoma, 85.7% in osteosarcoma, and 80.7% in chondrosarcoma. As regards limb function, 60 of 73 patients (88%) with a primary tumor in the lower extremity or pelvis could walk without any support at the last follow-up; however, 3 patients needed a walking stick (mainly due to incomplete union) to preclude full weight-bearing [34].

Sharma et al. reported on 14 patients with malignant bone tumors, including 9 osteosarcomas around the knee joint, who underwent ECI with intramedullary cement. Two patients developed wound infections and were salvaged by additional treatment without removal of graft. One patient was not evaluated due to the contaminated margin and salvaged by rotationplasty. The mean MSTS was 88%. They concluded that ECI is a feasible technique with decent local control in a short-term follow-up [35].

1.3.2 Pasteurized bone

Pasteurized tumor-devitalized autograft is the method sterilizing the tumor-bearing bone by heating it to 60–65 °C for 30–40 min. Manabe et al. developed this method and first reported the clinical outcome in 25 cases. The mean follow-up was 52 months, and 76% of the grafts survived at the last follow-up. Graft-host bone junction union was eventually obtained in 77%, with a mean duration of 12 months. Infection ($n = 5$) and fracture ($n = 3$) occurred; however, no recurrence was identified [18]. Jeon et al. analyzed the outcome of 21 intercalary pasteurized bones in lower extremities, including 5 pediatric patients. Complications included non-union ($n = 5$; 23.8%), infection ($n = 3$, 14.3%), fracture ($n = 2$; 9.5%), and local recurrences unrelated to the graft ($n = 2$; 9.5%). The average union time was 15.5 months, and the union rate was 86% in 10 years. The 10-year graft survival was 74%. They concluded that this method was a useful intercalary reconstruction method with lower rates of complications [37].

Qu et al. later reported on 27 patients (mean age of 28.3 (range, 9–73 years)) with intercalary reconstruction. Bony union was achieved in 92% of cases, with a mean duration of 11 months. Complications that needed additional surgery were non-union in junctions ($n = 4$; 7.4%), fracture ($n = 1$; 3.7%), infection ($n = 3$; 11.1%), and fixation failure ($n = 2$; 7.4%). The mean MSTS score was 93%. They concluded that their results of the favorable graft-host bone union and acceptable complication rates could consider this method as a useful intercalary reconstruction method [38].

Ikuta et al. reported the outcome of 24 cases treated by the modified heat-treated tumor-devitalized autograft reconstruction (70 °C for 15 min). Their study included 16 pediatric patients, and 17 reconstructions were combined with vascularized fibula grafts (VFGs). Eighteen graft-related complications (75%) were identified, including non-union ($n = 14$; 58%), infection ($n = 3$; 13%), bone absorption ($n = 5$; 21%), and fracture ($n = 1$; 4%). Sixteen complications (67%) were managed by additional surgery. Three patients (13%) had local recurrence from the surrounding soft tissue. Graft survival reached 70.1% in 10 years. In the univariate analysis, the upper extremity, intercalary grafts without VFG, and junction at the diaphyseal site were risk factors of non-union. In the multivariate analysis, upper extremity reconstruction was identified as an independent factor for non-union. They concluded that their modified technique could be a useful option for intercalary reconstruction with an appropriate selection of patients [39].

1.3.3 Frozen autograft

Cryosurgery for bone tumors was first described in 1969 by Marcove et al. in the management of bone tumors, for which it was used as a palliative procedure [53]. Marcove also reported the adjuvant treatment by filling the cavity, after the curettage of benign bone tumor, with liquid nitrogen [54]. Tsuchiya et al. developed a massive frozen autograft based on *in vitro* and *in vivo* analysis [55]. The entire tumor-bearing bone was treated by liquid nitrogen (− 196 °C) for 20 min, which causes ice crystal formation, cell dehydration, and subsequently cell death. Tsuchiya developed 2 related techniques, namely "free freezing" [15] and "pedicle freezing" [56].

The "free freezing" technique involves *completely* detaching the diseased bone, freezing it, and reattaching it (Fig. 3a). Specifically, after the exposure of tumor-containing tissue with an adequate margin, a K-wire is

inserted through the planned osteotomy line under fluoroscopy. Then, *en bloc* tumor excision is performed using a microsurgical saw. Soft tissues of the specimen are peeled, and the bony lesion of the tumor is curetted before freezing. The specimen is then treated for 20 min in liquid nitrogen that was stored in a sterilized flask right before freezing, thawed at room temperature for 15 min, and placed in distilled water containing 1% iodine for another 15 min. The frozen autograft is used for reconstruction with double or triple locking plates, and 2–3 screws are inserted into the epiphysis for stabilization. In cases of proximal tibial osteosarcoma, screw and spike washer are used to reattach the patellar tendon to the frozen autograft.

The "pedicle freezing" technique involves exposing the diseased bone *without completely removing it*, freezing it, and reattaching it (Fig. 3b). Figure 4 demonstrates this technique used in a 10-year-old girl with tibial osteosarcoma. The proximal part of the tumor was exposed with an adequate surgical margin, and osteotomy was then performed. Surrounding basal soft tissues were carefully protected with surgical sheets, and the proximal part of the tumor was elevated following isolation using cast padding soft rolls, an Esmarch bandage, and layers of surgical sheets to prevent not only tumor contamination but also frostbite of the surrounding normal tissue during freezing. Then, the intramedullary canal was subsequently curetted to remove the bone marrow containing the tumor tissue to prevent graft fracture caused by water expansion during freezing. The isolated tumor-containing bony specimen was then carefully rotated and placed in a container filled with liquid nitrogen for 20 min. After thawing, reconstruction was performed in the same procedure with the free freezing technique.

Igarashi et al. reviewed 36 cases of malignant bone tumor treated by frozen autografts, with a mean follow-up of 101 months. Although 11 complications (50%) occurred, including non-union ($n = 3$; 8.3%), infection ($n = 4$; 11.1%), fracture ($n = 7$; 19.4%), and local recurrences unrelated to the frozen bone ($n = 4$; 11.1%), the graft survival was 80.6%. The graft failures were occured in 7 cases of osteoarticular grafts [40]. In another study, Wu et al. compared 78 cases treated by ECI autografts with 85 cases treated by frozen autografts. The incidence of complications in ECI was 33.3% (26 cases), including 8 non-union (10.3%), 6 infection (7.7%), and 12 recurrence (15.4%) cases and that in frozen autograft was 27.1%, including 11 non-union (12.9%), 4 infection (4.7%), and 9 recurrence (10.6%) cases. However, no significant difference was found [36]. Moreover, Shimozaki et al. compared the outcomes of the pedicle freezing procedure ($n = 13$) and free freezing procedure ($n = 7$) in patients who underwent reconstruction in the lower extremities. The duration of graft-host bone junction union was significantly shorter, and the rate of postoperative complications was significantly lower, in cases with pedicle freezing than in those with free freezing. They speculated that the early recovery of blood flow might contribute to the favorable outcome in pedicle freezing [41].

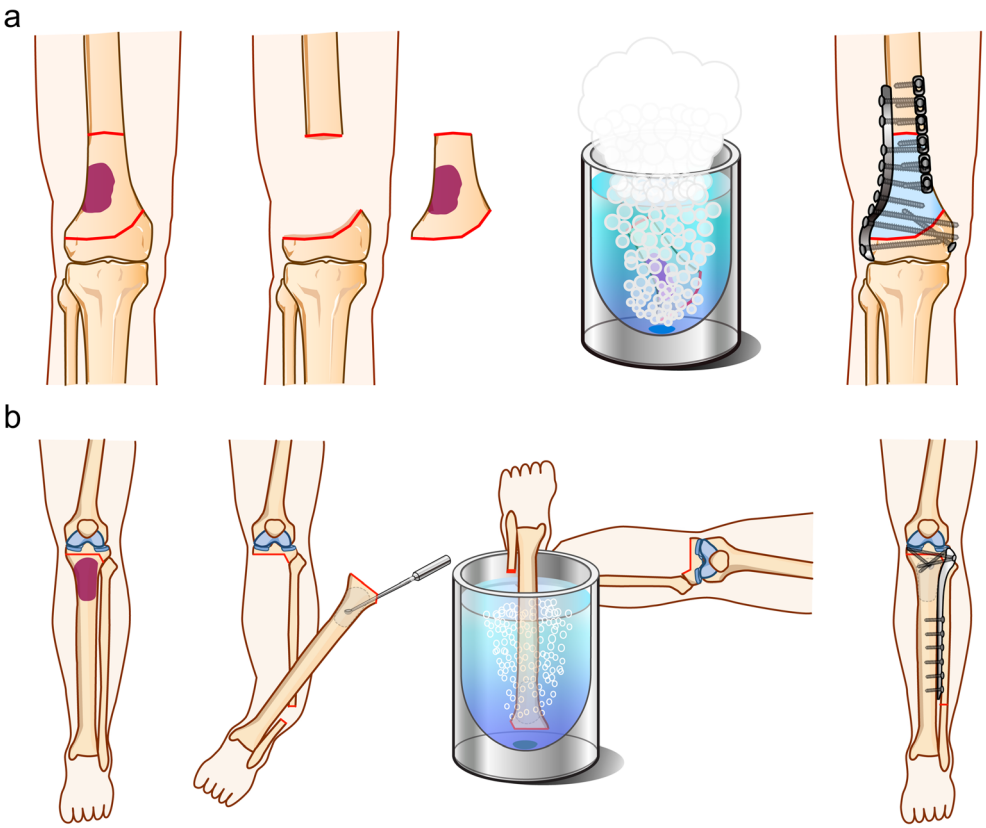

Fig. 3 Schema of the 2 surgical techniques used for tumor devitalization of autografts *via* liquid nitrogen. **a** *Free freezing*: the distal femur tumor is excised by epiphysis-preserving intercalary osteotomy; after freezing in liquid nitrogen for 20 min, osteosynthesis using plates and screws is performed. **b** *Pedicle freezing*: the proximal tibial tumor is excised by one-site osteotomy, the proximal part of the tumor is elevated, and the intramedullary canal that contains the tumor is subsequently curetted. The isolated bony specimen is carefully rotated and placed in liquid nitrogen for 20 min. Osteosynthesis using a plate and screws is then performed

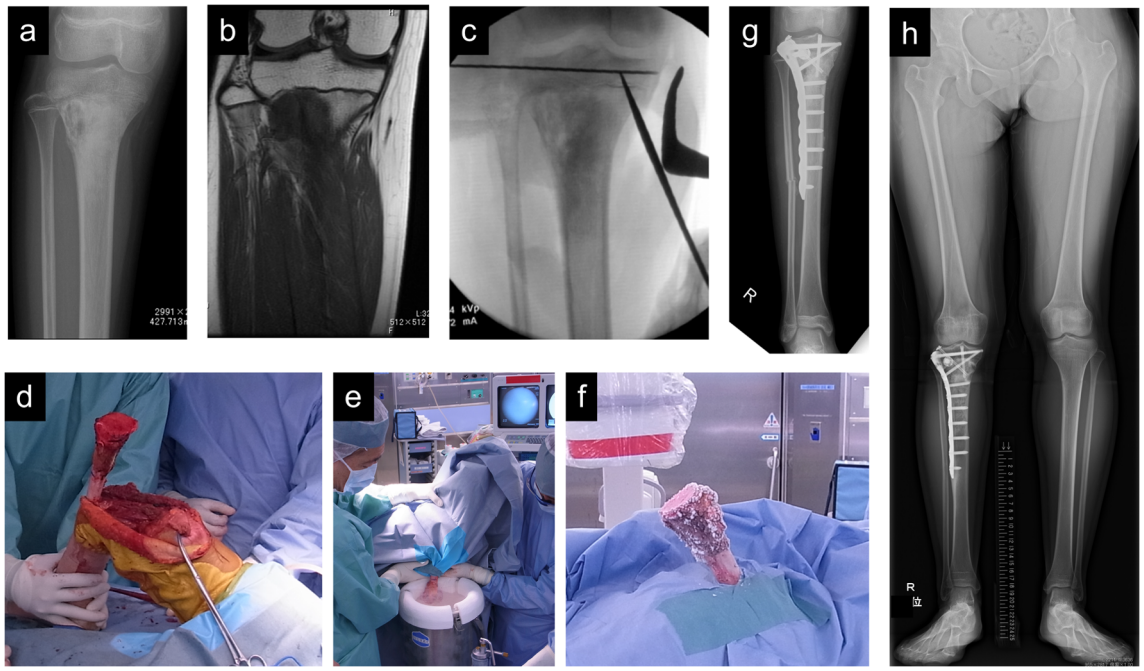

Fig. 4 A 10-year-old girl with osteosarcoma of the right proximal tibia. Preoperative plain radiograph (**a**) and T1-weighted magnetic resonance image (**b**). An intraoperative radiograph from image intensifier after K-wire insertion for transepiphyseal excision (**c**). A photograph of the diseased bone after transepiphyseal osteotomy (**d**). The bony lesion connecting with the limb was rotated and frozen in liquid nitrogen (**e**). Tumor-devitalized autograft after freezing (**f**). Plain radiographs immediately after the surgery (**g**) and 58 months later (**h**)

The authors of the present study reviewed 12 patients with pediatric osteosarcoma who underwent JPS (8 distal femora and 4 proximal tibias) with frozen autografts. The mean patient age was 11 years, and the mean follow-up period was 63 months. The present authors analyzed the growth of the residual epiphysis, and the mean epiphysis growth rate was 12.6% (range, 3.3–28.0%) in the affected side and 12.7% (range, 3.8–28.9%) in the contralateral side, without collapse of the residual epiphysis. The mean LLD was 26 mm, and 2 patients underwent an additional limb-lengthening surgery. The mean MSTS score at the last follow-up was 27.7. The present authors concluded that the growth of the residual epiphysis greatly influenced the JPS indication for pediatric osteosarcoma, although careful assessment for epiphyseal tumor involvement was mandatory [23].

A frozen autograft has more advantages, as it could preserve bone morphogenetic protein [57] and induce cryoimmunology [58–60]. Nishida et al. reported a case of metastatic femoral renal cell tumor with reduced multiple lung metastases following tumor excision and frozen autograft [60]. The serum levels of interferon-gamma and interleukin-12, which could stimulate the immunosystem [61, 62], increased after surgery. This phenomenon is called the abscopal effect, which refers to the regression of metastasis after radiation therapy for a local tumor [63]. Further analysis is required to reveal the immunological reaction following a frozen autograft.

1.4 Free vascularized fibula graft

Free vascularized fibula graft (FVFG) has the following advantages: it retains the ability of the living bone to hypertrophy, there is absence of resorption, and it maintains mechanical strength [64]. Taylor et al. first described this technique for trauma in 1975 [65], and Weiland et al. applied this technique for reconstruction following tumor excision in 1977 [66]. With FVFG, the hypertrophic change takes several years to complete in order to allow full weight-bearing; therefore, patients have to use crutches for a long period. Non-union, stress fracture, infection, and malunion have also been reported as complications [67]. Eward et al. reviewed 30 patients who underwent FVFG for large bony defects following tumor resections. Primary union was obtained in 23 (77%), within a mean duration of 6 months. Seven patients (23%) needed additional surgery for delayed union by revised fixation and bone grafting and eventually achieved secondary union, within the mean subsequent duration of 9.2 months. The most frequent complications were fracture (20%) and infection (10%). They considered FVFG as a reliable method despite its high complication rate [42].

Kiss et al. reported 5 pediatric cases (mean age 11.2 years) of FVFG following epiphysis-preserving resection for malignant proximal tibial tumors. The bony defect of the tibia was reconstructed with both the ipsilateral and contralateral fibulas. The fracture of the transplanted opposite side fibula was

detected in 3 patients (60%). Chronic osteomyelitis developed at the transplanted fibula in one patient (20%). Two patients could walk without support, and 3 patients could walk with full loading of the limb with orthoses. They concluded that FVFG could preserve the knee joint and that preserved knee joint could produce better function despite the difficulty in the fixation of a small proximal epiphysis [16].

Manfrini et al. reported the reconstruction of the proximal femur and hip joint using FVFG as treatment of an Ewing sarcoma in a 4-year-old girl, including the proximal joint cartilage with the open physis combined with a massive allograft. The patient showed successful continuous growth of the fibular head as well as successful longitudinal growth [68]. Stevenson et al. reviewed 11 children who underwent a vascularized fibular epiphyseal transfer for proximal humeral reconstruction following resection of primary sarcoma. Thirteen complications were identified, including 7 fractures and 4 transient nerve palsies, and 2 patients developed avascular necrosis of the graft. Hypertrophy and axial growth were evident in 9 patients (81.8%) who did not have avascular necrosis of the graft. The mean MSTS score was 77%. They concluded that a vascularized fibular epiphyseal transfer is recommended to patients who were considered unsuitable for tumor prosthesis because of very young age or an isolated diaphyseal tumor, despite the high incidence of complications including fractures [43]. Petersen MM et al. reviewed 8 cases with bone sarcoma reconstructed with FVFG. Their results included fracture in 4 cases, non-union in one case, pseudoarthrosis in one case, and hip dislocation in one case. They concluded their results were acceptable, although fracture was most frequent complication [69].

1.5 Distraction osteogenesis

DO is one of the biological methods utilized to reconstruct the bony defect with regenerative bone formation using an external fixator [17]. Figure 5 demonstrates this technique used in a 12-year-old boy with tibial osteosarcoma. With the expandable intramedullary nail, a less-invasive approach has been developed [70]. Tsuchiya et al. reported 11 cases, including 6 pediatric patients (mean age 21.5 years) with osteosarcoma around the knee treated by DO following intraepiphyseal excision. Although 7 complications, including pes equinus, fracture, superficial infection, peroneal nerve palsy, deep infection, delayed healing, and delayed union of the docking site, were recorded, all of them were managed by additional treatment. The mean MSTS score was 97.8% (10 cases were rated as 100% normal and 1 case as 77% normal). Ten patients achieved a full range of knee movement, whereas 1 patient has flexion limited to 0 to 50°. All patients resumed recreational activities without restriction. They thus concluded that DO as treatment of metaphyseal osteosarcomas around

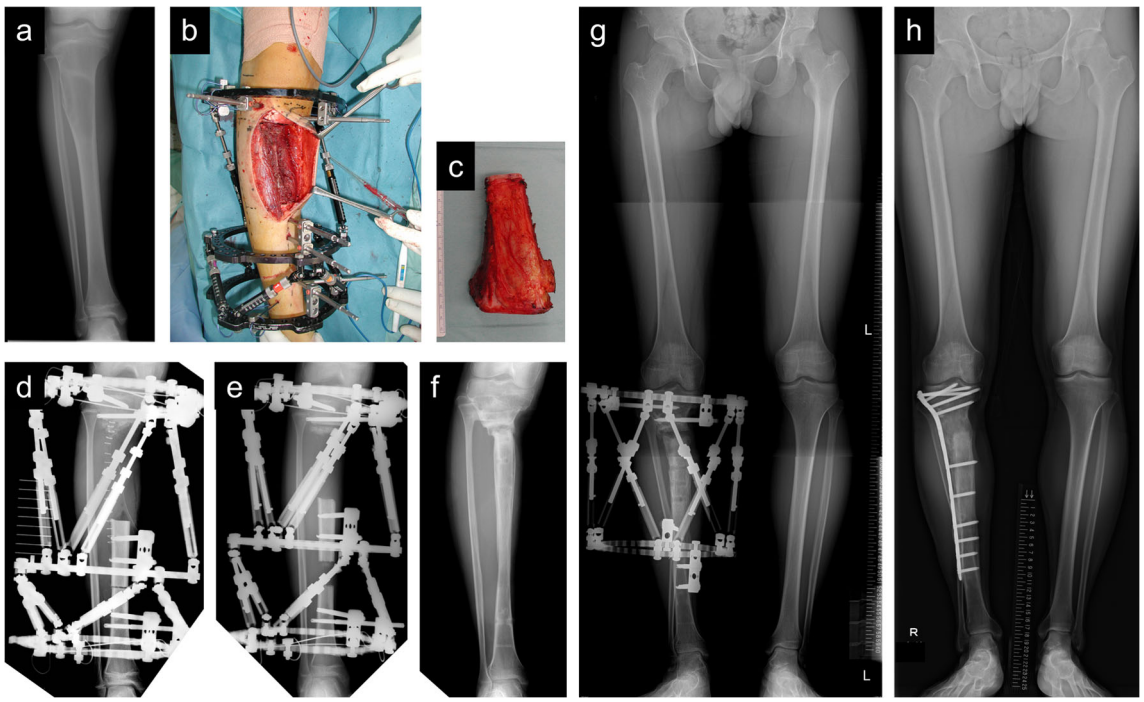

Fig. 5 A 12-year-old boy with osteosarcoma of the right proximal tibia. **a** Preoperative plain radiograph. A photograph after tumor excision and following the application of a **b** Taylor spatial frame and of the **c** tumor specimen. Plain radiographs recorded immediately **d** after the surgery, **e** 2 months after the surgery, **f** and 18 months after the surgery. The Taylor spatial frame is removed in **f**, and callus formation is visible. **g** Plain radiograph 41 months after the surgery. The Taylor spatial frame is re-applied to correct the deformity. **h** Plain radiograph 9 years after the final surgery, showing **h** excellent alignment and well-preserved residual epiphysis

the knee could provide excellent functional results if JPS was possible [17].

Demiralp et al. reported 13 patients who underwent reconstruction of bony defects (mean 14.6 cm) with Ilizarov DO following *en bloc* resection of bone tumors, with a mean follow-up period of 157 months. The mean MSTS score was 89.5% at the last follow-up. They also evaluated function using Knee Society Scale scores, and the mean score was 74.3. The mean foot and ankle disability index was used to evaluate tumors around the ankle joint, with a mean score of 81. The most frequent complications were pin tract infection (69%) and reduced range of motion (38%). They thus concluded that reconstruction with DO could be an efficient method in patients with long life expectancies, despite the high complication rate in a short-term follow-up [44].

Watanabe et al. reported the long-term outcomes of 22 patients who underwent joint-preserving tumor excision and reconstruction by DO for primary bone tumors in the lower leg and who were followed up for at least 10 years. Their study included 11 pediatric patients and 7 cases of osteosarcoma. Seven complications including delayed union ($n = 5$), delayed consolidation ($n = 4$), callus fracture ($n = 2$), and premature consolidation, pin tract infection, joint contracture, peroneal nerve palsy, and tumor recurrence with 1 case each, were managed by additional surgery. The MSTS score was 91.5% (range, 67–100%), with a mean follow-up of 202 months. They concluded that the long-term outcome of the reconstruction by the DO was fully satisfactory, although it required time and effort [45].

The DO can be also performed for physeal distraction for JPS in malignant metaphyseal bone tumors to gain a safe margin. The technique was first described by Cañadell et al. [71]. Betx et al. reported 6 pediatric patients with primary malignant metaphyseal bone tumors who underwent physeal distraction, and they found no local recurrences. The mean MSTS score was 79%. One major complication was an infection that needed transtibial amputation. They concluded that physeal distraction (Cañadell's technique) is a useful method in case of malignant tumors that are close to an open physis [72].

1.6 Custom-made implant

Custom-designed knee-sparing prostheses have been developed to reconstruct the bony defect with small adjacent joint surface in malignant bone sarcomas [46, 48]. Gupta et al. reported their preliminary results of 8 pediatric patients (mean age 17.4 years) with primary bone tumors of the distal femur, who underwent custom-made joint-sparing endoprosthesis reconstruction. The mean follow-up period was 24 (range, 20–31) months. One patient underwent reconstruction with an endoprosthesis, including a non-invasive expandable component and lengthened to 46 mm. The patient developed septicemia, but recovered well. The mean knee flexion was 102° (range, 20 to 120°), and the mean MSTS score was 24 (range, 20–28) at the last follow-up [46].

Spiegelberg et al. reported the early results of using a joint-sparing proximal tibial custom-made prosthesis for 8 primary bone tumors. In the design of each implant, the proximal and distal transection points had been determined by inspection of preoperative MR images and then designed by computed tomography to ensure accurate dimensions. In their study, the mean patient age was 28.9 (range, 8–43) years, and the mean follow-up was 35 (range, 4–48) months. The mean MSTS score was 79% (range, 57–90%), and the mean knee flexion was 112° (range, 100–120°). Local recurrence occurred in 1 patient and salvaged by a transtibial amputation. One periprosthetic fracture resulted in a painful malunion and eventually revised to a further knee endoprosthesis. They concluded that their preliminary results were satisfactory within the short term [47].

Agarwal et al. reviewed 6 patients with a customized diaphyseal implant. Three of these custom implants were equipped with an expandable (one minimally invasive and 2 non-invasive) mechanism to resolve LLD. Only 1 patient showed knee flexion restricted to 100°. They concluded that diaphyseal implants allowed immediate weight-bearing postoperatively. However, they were expensive, and their long-term results were not yet clarified. They proposed the most suitable expandable implants for cases in which the physis was resected and limb length needed to be managed [48].

Wong et al. reviewed 6 cases including 4 pediatric patients who underwent joint-sparing tumor excision under image-guided computer navigation and reconstruction with a custom-made joint-preserving prosthesis. The mean patient age was 17 (range, 6–46) years, and the mean follow-up period was 41 (range, 25–60) months. They described that the resected bones matched the prosthesis templates and fitted to the prostheses within ≤ 2 mm in any dimension. Histologic examination of all resected specimens revealed a negative tumor margin. The mean MSTS score was 29.1 (range, 28–30). The mean knee flexion was 115° (range, 90–130°). Although 1 patient with multi-planar bone resection for the distal femur developed aseptic loosening at the stem of the proximal femur component at 2.5 years after surgery and underwent revision with the proximal component alone, no postoperative wound infection, no failure of bony reconstruction, and no local recurrence were identified. Bone scans revealed no osteonecrosis in the residual epiphysis. Moreover, they presented a case with continuous growth of the residual epiphysis at the distal femur. Two patients with extendable prostheses had gained lengthening of 34 and 15 mm following a minimally invasive procedure. They concluded that the computer-assisted approach facilitated precise planning, execution of joint-sparing tumor resection, and reconstruction in their limited cases, although further longer follow-up assessment in a larger study population was warranted [12].

2 Conclusions

In this review, we discussed various joint-preservation bone reconstruction methods, including biological and non-biological methods. Joint-preservation surgery (JPS) has some advantages compared with joint-replacement surgery that uses a megaprosthesis. For instance, JPS maintains the adjacent joint and preserves the growth of the residual epiphysis, which provides excellent limb function. However, precise tumor excision with a close margin is mandatory to preserve the articular end of the affected bone. Thus, careful assessment of the tumor extension prior to and during JPS is critical. For skeletally immature children indicated for JPS, growth-related complications such as LLD should be considered. Although biological reconstruction methods need additional lengthening, the custom-made implant could resolve the LLD. Moreover, JPS is a complicated procedure, with various complications including infection, fracture, and loosening, but most of these complications could be managed by an additional procedure. Moreover, joint replacement using prosthesis is possible after failure of JPS. Although careful assessment of tumor involvement in the epiphysis, meticulous surgical procedure, and postoperative management is necessary, JPS enables preservation of the adjacent joint and continuous growth of the residual epiphysis, which provide excellent limb function. It is our opinion that the further analysis by multi-institutional setting is necessary to clarify long-term outcomes and establish global guidelines on the indication and surgical procedure for JPS.

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