CLINICAL ARTICLE

Impacts of Tumor Location, Nature and Bone Destruction of Extremity Osteosarcoma on Selection of Limb Salvage Operative Procedure

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Objective: To study the impacts of tumor location, nature and extent of bone destruction on selection of operative protocol for extremity osteosarcoma (OS).

Methods: The medical records of 201 patients with extremity OS treated in our institute from December 1999 to June 2014 were retrospectively reviewed. Ninety eligible patients (56 males and 34 females) of average age 20 ± 11 years (range, 4–40 years) were enrolled. Tumor locations were categorized as diaphyseal (4; diaphysis group) or juxta-articular (86); the latter being subclassified as with (51, type III, epiphysis group) or without invasion beyond the epiphyseal line or plate (35, type I and II, metaphysis group) according to MRI images. Tumor nature (osteogenic, 51; osteolytic, 39) was determined radiologically. Extent of bone destruction was quantitated according to Mirel's scoring system to obtain an "invasion score". Regular postoperative follow-up included physical examination and imaging evaluation.

Results: Fifty-four patients underwent biological reconstruction and 36 mechanical reconstruction. The mean follow-up duration was 51 months (range, 6–176 months, including four deaths within 12 months). Biological reconstruction was performed more frequently in the diaphysis and metaphysis groups (31/39, 79.5%) than mechanical reconstruction (8/39, 20.5%, $P < 0.05$). Biological reconstruction and articular preservation were associated with more satisfactory limb function (MSTS scores: 25.0 ± 3.3 and 25.1 ± 3.6) than mechanical reconstruction and articular resection (MSTS scores: 23.4 ± 3.7 and 23.1 ± 3.4 , $P < 0.05$). Reconstruction methods and articular preservation had no relationship with overall or tumor-free survival ($P > 0.05$). Osteolytic lesions were associated with more extensive bone destruction than osteogenic lesions according to invasion scores ($P < 0.05$). Following biological reconstruction, high invasion scores (>8) had a 13.5-fold risk of fracture compared with low scores (≤ 8) ($P < 0.05$). Twenty-one subjects had recurrences, 30 metastases and 26 died. Postoperative complications included infection (6), fracture (10), and prosthesis loosening (4). Kaplan-Meier analysis indicated 5- and 10-year survival rates of 68.9% and 62.8%, respectively, and 5- and 10-year tumor-free survival rates of 66.7% and 57.8%, respectively.

Conclusion: Selection of limb salvage operative protocol for extremity OS should rely on tumor location, nature and extent of bone destruction. Regardless of tumor site, mechanical reconstruction is indicated for tumors with high invasion scores (>8), whereas biological reconstruction is preferred for those with low invasion scores (≤ 8). Tumors sparing the epiphyseal line or plate are ideal candidates for articular preservation.

Key words: Limb salvage; Oncology; Osteosarcoma; Reconstruction; Surgery

Introduction

Osteosarcoma (OS) is one of the most common primary malignant tumors originating from bone. With

improved understanding of chemotherapeutic regimens and surgical techniques, treatment of OS has been modernized, the current long-term survival rates of patients with OS

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being reportedly up to 60%–70%^{1–5}. The current mainstay of OS treatment, limb salvage surgery, is feasible in 90% of subjects with OS^{6,7}. The aim of treatment of OS is not only to prolong life expectancy, but also to preserve limb function and improve patients' postoperative quality of life.

Limb-salvage procedures for OS involve wide resection of tumor and biological/mechanical reconstruction; however, because of its varying clinical manifestations, there is no optimal surgical procedure for OS^{8–10}. Biological reconstructive methods include autologous/allogeneic bone grafting and inactivated autograft replantation; frequently used inactivating methods involve alcohol, liquid nitrogen, pasteurization and microwave^{8,11–14}. The strengths of biological reconstruction include preservation of limb function, simplicity of procedures and acceptable cost. Additionally, according to recently published reports, immunological responses aroused by inactivated tumor cells may be favorable for OS patients' survival^{11–17}. Nevertheless, complications following biological reconstruction are not negligible, including infection, fracture, bone nonunion and limb length discrepancy (Fig. 1)^{11–17}. Mechanical reconstructive methods rely on prostheses to fill bone defects; advantages of such procedures include ideal resection margin and early postoperative ambulatory exercise. However, with prolonged follow-up, the risk of prosthesis-related complications such as prosthesis loosening, fracture and infection increases^{13,18–21}. Because bone defects in such cases are usually mainly attributable to the primary surgical procedure, it is characteristically extremely difficult to perform revision surgery for these complications^{22,23}.

There are some well recognized principles regarding the surgical treatment of extremity OS. Limb salvage procedures are strongly indicated for tumors staged as I, IIA and IIB according to the Enneking staging system that have responded well to chemotherapy, whereas encasement of major vessels and nerves by OS contraindicates limb salvage operation^{22–24}. Wide resection of tumor is mandatory for stage I OS, whereas more radical procedures are considered necessary for OS rated as stage II or higher²⁵. Nowadays, clinicians can choose from a variety of reconstructive methods for performing limb sparing procedures and often select a procedure based on personal experience and preference. However, ignoring or failing to meticulously assess factors such as tumor location, nature and extent of bone destruction can lead to selection of an inappropriate surgical procedure and result in unfavorable therapeutic outcomes²⁶. We reviewed the records of OS patients who had undergone limb salvage surgery in our institute (i) to determine the impacts of location, nature and bone destruction on selection of operative procedure, (ii) to help clinicians assess their patients' characteristics systematically, and (iii) to identify optimal operative procedures for various scenarios.

Materials and Methods

Inclusion and Exclusion Criteria

Inclusion criteria were as follows: (i) diagnosis of OS determined by pathologic examination; (ii) complete imaging examination; (iii) age at diagnosis ≤ 40 years; (iv) standard treatment comprising neoadjuvant chemotherapy and limb-

Fig. 1 An eight-year-old girl presented with osteosarcoma in her right distal femur. (A) MRI showing the mass is not invading the epiphysis. (B) The patient underwent alcohol inactivated autograft replantation and plate internal fixation. (C) A lower extremity length discrepancy was noted 37 months postoperatively, the right limb being 8 cm shorter than the left. (D) The limb length discrepancy was resolved 1 year after bone distraction had been performed. Thus, biological reconstruction allowed easy and effective treatment of postoperative limb length discrepancy in this patients because bone and joint structures had been preserved.

salvage operation; and (v) follow-up period at least 12 months (including postoperative death within 1 year).

Exclusion criteria were as follows: (i) recurrence or metastasis noted on diagnosis; (ii) tumor location axial or in the fibula alone; (iii) age at diagnosis >40 years; (iv) lost to follow-up; and (v) primary surgical procedure amputation rather than limb salvage surgery.

Patients

The medical records of 201 patients with extremity OS treated in our institute from December 1999 to June 2014 were retrospectively reviewed and 90 eligible patients enrolled, including 56 males and 34 females of average age 20 ± 11 years (range, 4–40 years). Recorded symptoms included pain and limb dysfunction lasting for 1–6 months. Seven subjects had pathologic fractures at the time of diagnosis. Metastasis was excluded by bone scanning and lung CT. Diagnosis of OS was determined by pathologic examination of an incision (12) or aspiration biopsy (78). Neoadjuvant chemotherapy regimens included cisplatin, doxorubicin and ifosfamide in accordance with a previously published report²⁷. According to the Enneking staging system, there were two IIA (2.2%) and 88 IIB (97.8%) tumors. Their locations included the femur (52, 57.8%), tibia (29, 32.2%), humerus (8, 8.9%) and radius (1, 1.1%)²⁸.

Evaluation of Tumor Location, Nature and Extent of Bone Destruction

Evaluation of Tumor Location

Bone destruction and formation of soft tissue masses were assessed by preoperative plain X-ray films, MRI and CT, and tumor borders were identified by MRI. Patients with juxta-articular OS were categorized into three groups in accordance with the San-Julian classification system and the relationship between tumor border and epiphyseal line or plate demonstrated by MRI (MR classification criteria). As shown in Fig. 2,

type I denotes that the tumor border has not invaded beyond the epiphyseal line or plate and is ≥ 1 cm from it, type II denotes that tumor border is <1 cm from the epiphyseal line or plate, and type III indicates tumor has invaded beyond the epiphyseal line or plate²⁹. According to these criteria, there were 7 type I (7.8%), 28 type II (31.1%), and 51 type III (56.7%) OS. Besides the aforementioned 86 juxta-articular OS, four cases had diaphyseal OS (4.4%). To facilitate clinical analysis, the patients were classified into diaphysis (4, 4.4%), metaphysis (35, including type I and II, 38.9%), and epiphysis groups (51, type III, 56.7%). Because bone healing or osteosclerosis were noted in all subjects with pathologic fractures after preoperative chemotherapy, these cases were not categorized as type III.

Evaluation of Tumor Nature

Preoperative X-ray and CT were used to evaluate tumors as osteogenic (51, 56.7%) or osteolytic (39, 43.3%). Mixed bone destruction (with both osteogenic and osteolytic lesions) was noted in 29 cases (32.2%). These tumors were classified according to their major imaging presentation (mostly osteogenic or osteolytic), which resulted in 17 of the lesions with mixed destruction (18.9%) being classified as osteogenic and 12 (13.3%) as osteolytic.

Extent of Bone Destruction

X-ray, CT and MRI were utilized to evaluate the extent of bone destruction. In accordance with Mirel's scoring system, tumor location, nature, pain, and tumor length and transverse diameter were used to calculate an invasion score to provide a quantitative measure of bone destruction (Table 1)³⁰. The transverse diameters of tumor were classified as $> \frac{1}{2}$ and $< \frac{1}{2}$ the circumference of the diaphysis and the lengths of tumor as $> \frac{1}{3}$ and $< \frac{1}{3}$ the length of the diaphysis. The total possible score is 12. The average scores of patients in our cohort were 8.4 ± 1.3 (range, 6–12).

Fig. 2 Locations of extremity osteosarcomas. Patients with major invasion of tumor across the diaphysis were classified as “diaphysis”. “Type I” denotes tumor border does not invade beyond the epiphyseal line or plate and is at least ≥ 1 cm from these structures; “Type II” denotes tumor is <1 cm from the epiphyseal line or plate; and “Type III” denotes tumor is invading beyond the epiphyseal line or plate.

TABLE 1 Invasion score for evaluating bone destruction by osteolytic osteosarcoma

Variable	Score		
	1	2	3
Location	Upper limb	Lower limb	Peritrochanter
Nature	Osteogenic	Osteolytic	—
Pain	Mild	Moderate	Severe
Transverse diameter	Small*	Large†	—
Length	Small‡	Large§	—

*Small denotes transverse diameter of tumor < ½ the diaphysis circumference.
†Large denotes diameter >½ the circumference.
‡Small denotes tumor length <½ diaphysis length.
§Large denotes the length >½ the diaphysis length.

Operative Procedures

As shown in Figure 3, 34 patients underwent mechanical reconstruction (29 prostheses and five autograft-prosthesis composite), whereas 56 patients underwent biological

reconstruction. Biological reconstruction methods included alcohol inactivated autograft replantation (AAR) without articular preservation (23), AAR with articular preservation (20), *in situ* microwave ablation (9), bone distraction (1), allogeneic bone grafting with epiphyseal preservation (1) and autologous bone grafting (2). Fixation methods used in biological reconstruction included intramedullary nails (32), plates (20) and external fixator frame (4).

Follow up

Follow-up was performed in accordance with the National Comprehensive Cancer Network guidelines³¹. The content of follow-up included inquiry, physical examination, chest X-ray or CT, X-ray of surgical location and evaluation of limb function. Functional evaluation was conducted based on the Musculoskeletal Tumor Society (MSTS) criteria³².

Statistical Analysis

SPSS software (version 15.0, SPSS., Chicago, IL, USA) was used to perform statistical analysis, analysis of variance and Student's *t* test for consecutive data and Pearson's χ^2 test and Fisher's exact test for categorical data. Kaplan–Meier analysis

Fig. 3 Selection of operative procedure and prognosis of extremity osteosarcoma.

was used to analyze survival and prognosis, the significance level being set at P value <0.05 .

Results

Prognosis and Survival

Prognosis of patients is shown in Fig. 3. The average duration of follow-up was 51 months (range, 6–176 months), including four deaths within 12 months. By the end of follow-up, there were 21 recurrences (21/90, 23.3%), 30 metastases (30/90, 33.3%) and 26 deaths (26/90, 28.9%), nine cases surviving with tumor (9/90, 10%). Kaplan–Meier analysis indicated 5- and 10-year survival rates were 68.9% and 62.8%, respectively, and 5- and 10-year tumor-free survival rates 66.7% and 57.8%, respectively.

Postoperative Outcomes

Twenty-one patients had recurrences. Their subsequent treatments included amputation (4), wide resection of soft tissue tumor (4), prosthesis replacement (1) and *in situ* microwave ablation (1); the remaining 11 patients refused further treatment. Seven patients (7/90, 7.8%) underwent amputation, two for infection and five for recurrence. Postoperative fractures occurred in 10 patients (10/56, 17.9%) and four had prosthetic loosening (4/34, 11.8%). At the end of follow-up, the limb salvage rate was 75.6% (68/90); patients who had undergone biological and mechanical reconstruction had similar limb salvage rates (40/55, 72.7%; 28/35, 80.0%, respectively; $P > 0.05$).

Postoperative complications are listed in Fig. 3. Postoperative infection occurred in six patients (6/90, 6.7%),

3/34 who had undergone mechanical reconstruction (8.9%) and 3/56 who had undergone biological reconstruction (5.4%). Postoperative infection occurred in three patients who had undergone biological reconstruction (AAR, 1; microwave ablation, 2); reconstructive methods did not correlate with infection rates ($P > 0.05$). Notably, 2/3 (66.7%) of the postoperative infections following mechanical reconstruction led to amputation, whereas the infections following biological reconstruction were successfully treated by limb salvage surgery comprising debridement, drainage, negative pressure wound therapy and bone grafting, indicating that treatment of infection is more effective after biological than after mechanical reconstruction. Fracture and loosening rates were similar for the two reconstructive methods ($P > 0.05$). Ten fractures (Fig. 4) occurred after biological reconstruction; six after AAR with intramedullary nail fixation, three after AAR and microwave ablation with plate fixation and one after microwave ablation with external fixation. Postoperative fractures were treated by open reduction with internal fixation (9) or external plaster fixation (1). By the end of follow-up, average MSTS score of these 10 patients were 25.4 ± 2.3 (range, 23–30). No patient who had undergone mechanical reconstruction sustained a fracture. However, four cases had prosthetic loosening (4/34, 11.8%), all of whom underwent revision surgery. Their postoperative MSTS scores were 23.0 ± 5.4 (range, 16–30); thus one patient had poor limb function (postoperative MSTS score 16). Our findings indicate that treatment of fractures following biological reconstruction may result in better limb function than revision operations for prosthetic loosening after mechanical reconstruction.

Fig. 4 A 15-year-old boy presented with osteosarcoma of the left distal femur. (A) X-ray film showing considerable bone destruction and formation of a soft tissue mass. (B) A fracture occurred 8 months after alcohol-inactivated autograft replantation with preservation of epiphysis had been performed. (C) Intraoperative photograph during open reduction and internal fixation. (D) Postoperative X-ray film and (E, F) physical examination showing satisfactory postoperative outcomes after 82 months of follow-up, indicating fractures after biological reconstruction can be successfully treated and satisfactory postoperative function achieved by internal fixation.

Operative Procedures and Survival

Kaplan–Meier analysis indicated that 5- and 10-year survival rates of patients who had undergone biological reconstruction were 68.3% and 63.5%, respectively, and tumor-free survival rates 62.8% and 51.2%, respectively, whereas 5- and 10-year survival rates of those who had undergone mechanical reconstructions were 69.2% and 62.3%, respectively, and 5- and 10-year tumor-free survival rates 60.3% and 55.2%, respectively. No relationship between reconstructive method and survival was identified ($P < 0.05$). Five- and 10-year survival rates of patients who had undergone articular preserving surgery were 66.1% and 64.7%, respectively, and their 5- and 10-year tumor-free survival rates 72.9% and 53.2%, respectively. The 5- and 10-year survival rates of the patients who had not undergone articular preservation were 69.8% and 65.4%, respectively, and their 5- and 10-year tumor-free survival rates 57.6% and 52.5%, respectively. Log-rank tests identified no correlation between articular preservation and survival ($P > 0.05$). MSTs scores to quantify limb function were 25.0 ± 3.3 and 25.1 ± 3.6 after biological reconstruction and articular preservation, respectively. These outcomes are better than after mechanical reconstruction (MSTs scores 23.4 ± 3.7) and articular removal (23.1 ± 3.4), this difference being significant ($P < 0.05$), indicating that biological reconstruction and articular preservation are associated with better postoperative limb function. Our findings suggest that reconstructive methods have no relationship with tumor recurrence, metastasis and death, whereas biological reconstruction and procedures that preserve articular structures are associated with better limb function.

Impacts of Tumor Location on Selection of Operative Procedure

Tumor locations of OS and reconstructive methods are listed in Table 2 and Fig. 3. There were four patients in the diaphysis group, one of whom underwent total femur prosthesis replacement because of extensive tumor invasion (Fig. 5) and three biological reconstruction with articular preservation (AAR, 2; microwave ablation, 1). No recurrences were noted by the end of follow-up (range, 12–176 months). All 19 patients with MRI type II tumors underwent biological reconstruction with articular preservation (AAR, 13; epiphyseal distraction, microwave ablation and autologous fibular grafting, 2; *in situ* microwave ablation, 2; allogeneic bone grafting, 1; and bone distraction,

1). Three of these patients developed recurrences (3/19, 15.8%) by the end of follow-up (range, 12–138 months), all of which occurred after AAR. It was not possible to determine whether there was a correlation between recurrence and insufficient tumor resection margin. Fifty-one cases were classified as having MRI type III tumors (epiphysis group). The three of these who presented with intact subchondral structures according to MRI (invasion scores 8, 10, and 11) underwent *in situ* microwave ablation with articular preservation; no recurrences were noted over follow-ups of 12–16 months, indicating that microwave ablation may be feasible for patients with type III OS yet with intact subchondral structures. According to univariate analysis, the diaphysis and metaphysis groups more frequently underwent biological (31/39, 79.5%) than mechanical reconstruction (8/39, 20.5%); this difference is significant ($P < 0.05$).

Impact of Tumor Nature and Extent of Bone Destruction on Selection of Operative Procedure

Seven of the patients who subsequently sustained postoperative fractures following biological reconstructions had presented with osteolytic lesions (7/23, 30.4%), whereas only 3/32 with osteogenic lesions developed postoperative fractures (9.4%); this difference is significant ($P < 0.05$). The average invasion score for osteogenic lesions was 7.9 ± 0.9 (range, 6–9), which is significantly lower than that for osteolytic lesions (average, 9.2 ± 1.3 ; range, 7–12; $P < 0.05$), indicating that osteolytic lesions are associated with more extensive bone destruction. Only one of the patients who had undergone biological reconstruction and had low invasion scores (≤ 8) subsequently sustained a postoperative fracture (1/28, 3.6%), whereas nine cases with high invasion scores (> 8) had fractures (9/27, 33.3%); this difference is statistically significant ($OR = 13.5$, $P < 0.05$). Thus, according to our data, patients who have undergone biological reconstruction and had lesions with high invasion scores (> 8) are 13.5-fold more susceptible to postoperative fractures than those with low scores (≤ 8).

Considering osteolytic lesions were associated with more significant bone destruction, we evaluated the factors influencing postoperative fractures in patients with osteolytic lesions (Table 3). Seven osteolytic lesions with large transverse diameter ($> \frac{1}{2}$ the circumference of the diaphysis) sustained fractures (7/33, 21.2%), whereas none of those with shorter transverse diameters developed fractures ($P < 0.05$). Length of tumor was unrelated to incidence of postoperative

TABLE 2 Relationship between tumor location and surgical procedure (cases [%])

Tumor location	Reconstruction		P value	Articular preservation		P value
	Biological	Mechanical		Preserved	Not preserved	
Lesion not invading beyond epiphyseal line or plate*	31 (79.5)	8 (20.5)	0.02	28 (71.8)	11 (28.2)	0.00
Lesion invading beyond epiphyseal line or plate†	24 (47.1)	27 (52.9)		3 (5.9)‡	48 (94.1)	

* Denotes tumor invading across the diaphysis and lesion classified as MRI types I and II.

† Denotes tumor classified as MRI type III.

‡ Three cases with MRI type III tumor and intact subchondral structure underwent microwave ablation with articular preservation.

Fig. 5 (A) A 32-year-old man presented with osteosarcoma invading the whole diaphysis of left femur according to MRI. (B, C) Total femur prosthesis replacement was performed because of the extensive diaphyseal destruction evident on MRI. (D) Late-onset deep infection was detected 123 months postoperatively. (E, F) Debridement and negative pressure wound therapy was performed and intravenous antibiotics administered until adequate granulation had formed and there was no evidence of infection, when the wound was closed directly with suturing and the limb thus was successfully preserved.

fracture ($P > 0.05$). Four of the cases with preoperative pathological fractures (4/5, 80%) and three without them (3/18, 16.7%) had postoperative fractures after biological reconstruction ($OR = 20.0$, $P < 0.05$). Notably, all pathological fractures occurred in osteolytic lesions with average invasion scores of 10.7 ± 0.7 (range, 10–12), indicating significant bone destruction. Our findings suggest that osteolytic OS with significant bone destruction (invasion score > 8) and pathological fractures are associated with considerable risk of fractures after biological reconstruction.

Discussion

Although limb salvage operation is the mainstay of treatment of OS, the indications for articular preservation are still controversial. San-Julian *et al.* investigated the indications for varying operative procedures according to the relationship between tumor border and epiphyseal plate in children²⁹; we used classification criteria that are in accordance with theirs for both pediatric and adult patients with juxta-articular OS. According to our criteria, with type I and II tumors (metaphysis group) the tumor border does not invade beyond the epiphyseal line or plate, whereas with type III tumors

(epiphysis group) the tumor has invaded beyond these structures³³. Articular preservation is reportedly indicated for San-Julian type I tumors, whereas such surgical procedures are contraindicated for type III tumors³³. However, the optimal operative procedure for San-Julian type II tumors is controversial. Some authors suggest that articular preservation may not achieve a safe tumor resection margin in such cases, thus increasing their risk of recurrence³⁴. In our cohort, we divided tumor locations into three categories; namely diaphysis, metaphysis (MRI types I and II), and epiphysis (MRI type III). Patients classified as belonging to the diaphysis and metaphysis groups more frequently underwent biological reconstruction with articular preservation, partly because their tumors did not invade beyond the epiphyseal line or plate and partly because of the satisfactory effects of chemotherapy and development of surgical techniques (Fig. 6).

Comparison of Therapeutic Effects of Biological and Mechanical Reconstruction

The main operative procedures for OS involve biological and mechanical reconstruction, these two types of procedure having varying strengths and weaknesses. Biological

TABLE 3 Factors associated with postoperative fracture in osteolytic tumors following biological reconstruction (cases [%])

Factors	Fracture after biological reconstruction		P value
	Yes	No	
Osteolytic			
Yes	7 (30.4)	16 (69.6)	0.04
No	3 (9.4)	29 (90.6)	
Sex			
Male	6 (42.9)	8 (57.1)	0.18
Female	1 (11.1)	8 (88.9)	
Age			
≤18 years	3 (17.6)	14 (82.4)	0.04
>18 years	4 (66.7)	2 (22.3)	
Tumor transverse diameter			
>½ circumference	7 (38.9)	11 (61.1)	0.04
<½ circumference	0 (0)	5 (100)	
Tumor length			
>½ diaphysis length	2 (28.6)	5 (71.4)	0.65
<½ diaphysis length	5 (31.2)	11 (68.8)	
Pathological fracture			
Yes	4 (80.0)	1 (20.0)	0.02
No	3 (16.7)	15 (83.3)	
Fixation			
Intramedullary nail	2 (18.2)	9 (81.8)	0.38
Plate and external fixation	5 (41.7)	7 (58.3)	

reconstruction involves simpler procedures, lower costs with ideal preservation of function and acceptability to patients. However, postoperative recovery is prolonged, full weight bearing ambulation usually being delayed. In addition,

postoperative complications, including recurrence, fracture, infection and nonunion, are not negligible^{3-7,35-38}. Mechanical reconstruction can achieve ideal tumor resection margins and allow instant weight bearing ambulation postoperatively. Some authors have suggested that the short term prognosis of mechanical reconstruction outweighs that of biological reconstruction; however, prosthesis replacement requires complicated operative techniques and is costly. Additionally, with prolonged follow-up the risk of prosthesis-related complications such as prosthetic loosening, fracture and infection increases and revision operations can be extremely difficult because of the large bone defects caused by the primary procedure³⁹⁻⁴⁴. In our cohort, 34 patients underwent mechanical reconstruction and 56 biological reconstruction, including AAR (43), microwave ablation (9), autologous bone grafting (2), allogeneic bone grafting (1), and bone distraction (1). When we compared the survival and functional outcomes of patients who underwent different types of reconstruction (biological and mechanical reconstruction, articular preservation and articular removal), we found that biological reconstruction was not associated with an increased risk of negative events during long-term survival. Additionally, we found that patients who had undergone biological reconstruction and articular preservation had more favorable functional outcomes. Thus, according to our data, when performed in accordance with our indication criteria, reconstructive methods are safe and beneficial for patients with OS.

Treatment of postoperative complications following biological and mechanical reconstructions was varied.

Fig. 6 (A) A 15-year-old boy presented with osteosarcoma invading the epiphysis of the right distal femur according to MRI; the subchondral structure was intact. (B–D) This patient underwent *in situ* microwave ablation and internal fixation. (E) Postoperative X-ray film indicating absence of destruction or fracture of the right femur. (F, G) Limb function is acceptable. Thus, microwave ablation is feasible in some patients with type III OS and intact subchondral structure and enables better preservation of postoperative limb function.

Although patients who had undergone biological and mechanical reconstructions had similar infection rates, patients with infection who had undergone mechanical reconstruction more often required amputation, whereas similar conditions in patients who had undergone biological reconstruction were all treated successfully by limb salvage procedures. The two reconstructive methods had similar fracture rates and prosthetic loosening rates. Ten patients who had undergone biological reconstruction sustained postoperative fractures, one of which was treated by plaster fixation and the other nine by open reduction and internal fixation. The average postoperative MSTS score was 25.4 ± 2.3 (range, 23–30). All four subjects with prosthetic loosening required revision surgery, which was very difficult to perform because of the large bone defects resulting from the primary surgery. These patients' average postoperative MSTS score was 23.0 ± 5.4 (range, 16–30), including one case with poor limb function (MSTS score 16). Our findings indicate that biological reconstruction preserves functional structures rather than causing large bone defects, making secondary surgery less difficult and resulting in satisfactory limb function and limb salvage rates after secondary surgery.

Impact of Tumor Nature and Bone Destruction on Selection of Reconstruction Procedures

The rate of fracture, one of the commonest complications of biological reconstruction for OS, is reportedly 16%–27%⁴⁵. Postoperative fractures are likely partially attributable to the duration of bone healing after biological reconstruction, which is reportedly 6 months or longer; thus, early weight bearing ambulation and functional exercises may be associated with increased risk of fracture. Additionally, osteolytic lesions that have caused notable bone destruction may

contribute to patients' susceptibility to postoperative fracture³. However, because tumor nature and extent of bone destruction are not usually systematically evaluated in the process of selecting an operative procedure for patients with OS, biological reconstruction may be selected inappropriately, resulting in high fracture rates^{46–50}. In our cohort, we assessed bone destruction quantitatively and included tumor location, nature, pain, transverse diameter and length of tumor in our scoring criteria to create an invasion score. Our data indicate that, for patients undergoing biological reconstruction, invasion scores ≥ 8 are associated with a 13.5-fold increase in the risk of postoperative fracture compared with patients with lower scores. Additionally, pathological fractures (which imply significant bone destruction) are associated with increased risk of fracture after biological reconstruction ($OR = 20.0$, $P < 0.05$). All seven cases in our cohort who had pathological fractures at diagnosis had osteolytic lesions and high invasion scores (10–12). According to our findings, high invasion scores (>8) indicate extensive bone destruction that prejudices bone healing. We consider biological reconstruction contraindicated in such cases because of the considerable risk of postoperative fracture.

Indications for Biological and Mechanical Reconstruction for Extremity OS

A variety of diverse choices are available to clinicians selecting limb salvage procedures for extremity OS; unfortunately, these choices are usually based on personal experience and preference rather than on systematic and quantitative preoperative assessment⁵¹. Our findings indicate that surgical decisions should be based on tumor location, nature and extent of bone destruction, all of which should be systematically evaluated prior to surgical treatment.

Fig. 7 Strategy for selecting optimal procedure for extremity osteosarcoma. In the diaphysis and metaphysis groups, the tumor border does not invade beyond the epiphyseal line or plate, whereas in the epiphysis group, the tumor has invaded beyond these structures.

Fig. 8 (A) A 28-year-old man with osteosarcoma in the left distal femur underwent prosthesis replacement. (B, C) Mid-femur bone destruction and formation of a mass were detected by X-ray and CT 26 months postoperatively. (D) This patient underwent a secondary procedure with microwave ablation and preservation of the prosthesis. (E) Postoperative X-ray film showing a satisfactory therapeutic outcome. Thus, microwave ablation can be utilized as effective adjunctive treatment for local recurrence of OS while preserving the prosthesis.

We utilized MRI classification criteria and invasion scores to characterize the oncologic characteristics of each patient's OS and enable selection of optimal and individualized operative procedures. Based on our findings, we consider the indications for biological and mechanical reconstructions are as follows (Fig. 7). Biological reconstruction with articular preservation is indicated in patients with tumor borders not invading beyond the epiphyseal line or plate (diaphysis and metaphysis group) and low invasion scores (≤ 8), whereas we recommend mechanical reconstruction for patients with high invasion scores (>8), especially when paired with tumor borders exceeding epiphyseal line or plate (epiphysis group). In patients with tumors in the epiphysis category with lower invasion scores (≤ 8), biological reconstruction without articular preservation and mechanical reconstruction is feasible. Our findings suggested these indications of operation are safe and beneficial in patients with OS.

Other factors should also be taken into account when selecting operative procedures for patients with OS. In our cohort, we only enrolled patients younger than 40 years at diagnosis and excluded individuals with multiple lesions and recurrence at diagnosis. However, such cases are not rare in clinical practice (Fig. 8). It is therefore necessary to consider factors such as treatment purpose (palliative or radical), life expectancy, the condition of the soft tissue, and bone growth potential when selecting the optimal operative procedure.

Limitations of the Study

This is a single-center retrospective research and therefore subject to the limitations of such studies. Because the period over which patients were treated was long, the surgical techniques inevitably varied. There were also few patients and insufficient length of follow-up to evaluate some surgical techniques (such as microwave ablation). Large, multicenter, long-term trials are warranted in the future.

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