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ORIGINAL RESEARCH

Intercalary Allograft to Reconstruct Large-Segment Diaphysis Defects After Resection of Lower Extremity Malignant Bone Tumor

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Aim: To evaluate the clinical effect of intercalary allograft transplantation and reconstruction in the treatment of diaphyseal defect after resection of lower extremity malignant bone tumor.

Methods: Clinical data of 17 patients diagnosed with malignant lower-limb bone tumors and having undergone segmental allograft reconstruction with a mean follow-up of 49.8 (26–78) months were included. Segmental allografts of average 17-cm length preserved by deep-freezing were used and fixed using intramedullary nail, double plate, and intramedullary nail and plate combination in 2, 5, and 10 patients, respectively. Host–donor junctions were perfectly and roughly matched in 5 and 12 patients, respectively. Allograft union, local recurrence, and complications were assessed using clinical and radiological tests. Allograft union was evaluated using the International Society of Limb Salvage (ISOLS) scoring system. The functional prognosis was evaluated using the Musculoskeletal Tumour Society (MSTS) scoring system.

Results: Intercalary allograft reconstruction of femoral shaft, tibial shaft, and distal tibia with ankle arthrodesis was performed in eight, four, and five patients, respectively. Two patients had local recurrence and underwent amputation; one died of metastasis. Host–donor junctions in two patients showed nonunion; 12 patients achieved bone union. The average union time was 12.1 months. No allograft fracture or infection occurred. Union rates were 100% and 88.2% at metaphyseal and diaphyseal junctions, respectively. Healing time differed significantly between the precisely and roughly matched groups ($p<0.01$). The incidence of nonunion was higher after intramedullary nailing than after the other two methods ($p<0.05$). The mean MSTS score was 24.2 (14–29) at the end of follow-up.

Conclusion: Intercalary allograft transplantation is an effective strategy for diaphyseal defect following post-tumor resection in the lower extremity. Good bone healing after allograft reconstruction is achieved with stable internal fixation and perfectly matched host–donor interfaces.

Keywords: intercalary allograft, malignant bone tumor, bone healing, lower extremity, internal fixation

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Introduction

With the development of neoadjuvant chemotherapy, radiotherapy and targeted drug therapy in the clinical treatment of malignant bone tumors, limb salvage surgery has become the most important surgical method for malignant bone tumors. Limb salvage surgery includes two key techniques: radical resection of

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tumors and effective reconstruction of bone defects.[1] The commonly used methods for the reconstruction of bone defect after resection of tumor segment include artificial prosthesis,[2] allogeneic bone,[3,4] devitalized bone[5,6] and so on. The resection of malignant bone tumors located in the diaphysis tends to preserve their own joints, which is different from the metaphysis, but in many cases the residual bone at both ends is not enough to stabilize the metal prosthesis, which brings great difficulties to limb salvage.

Many literatures have reported[7–13] that intercalary allograft reconstructions following resection of malignant bone tumors in limb salvage is an alternative method, which can preserve joint function to the largest extend by maintaining articular cartilage and ligaments, and even preserving adjacent growth plates in adolescent patients. However, the potential complications such as nonunion, infection, allograft fracture, internal fixator failure, immune response and so on limit its widespread use.[10,14,15] Furthermore, there is disagreement regarding its clinical efficacy, with some studies showing very high failure rates to recommend this method.[3,14,16] The prognosis of this technique at different limb sites also varies.[15] Therefore, studies with a higher number of cases are required for more accurate conclusions.

Intercalary allograft has been used for diaphyseal defect reconstruction following malignant bone tumor resection at our center for 10 years. During long-term follow-up, we found differences in the clinical efficacy of this technique between application in the upper and lower extremity; however, the sample size of the upper-limb group was insufficient to evaluate curative outcomes. In this study, we retrospectively analyzed clinical data of patients who underwent lower-limb diaphyseal reconstruction with intercalary allografts following primary malignant bone tumor resection, objectively evaluated the oncology prognosis and functional prognosis, and analyzed the prognostic factors to provide evidence support for clinical treatment.

Patients and Methods

Patients

Patients with primary malignant bone tumors of lower extremities who underwent long-segment allograft bone transplantation in our Bone Tumor Center between August 2012 and November 2017 were enrolled in the study. There were 17 patients, nine males and eight females, with a mean age of 24.9 years (14 to 66). Diagnoses were confirmed on preoperative histopathological examination and included osteosarcoma (OS), chondrosarcoma (CS), ameloblastoma (AB), undifferentiated pleomorphic sarcoma (UDPS), and Ewing sarcoma (ES) in 12, 1, 1, 1, and 2 patients, respectively. The inclusion criteria were as follows: 1. Histopathological confirmed primary malignant bone tumors; 2. Tumors located in the lower extremity shaft, without involving important blood vessels and nerves; 3. Limb-salvage conditions for repairing bone defects with large allografts are available. 4. The patient's case data are complete and long-term follow-up is obtained. All patients underwent radiography, computed tomography (CT), magnetic resonance imaging (MRI) and bone scans preoperatively, and routine needle biopsy was performed to make a definite diagnosis. Neoadjuvant chemotherapy, post-operative chemotherapy, post-operative radiotherapy and targeted drug therapy were administered as needed. The clinical data including sex, age, location of tumors, length of bone grafts, surgical methods and types of internal fixation were recorded and analyzed (Supplement 1). The grade of tumors was assessed by Enneking staging of malignant bone tumors.[17] The study was conducted in accordance with the Declaration of Helsinki and approved by the Research Ethics Committee of Xiangya Hospital. All patients participating in the study received informed consent and signed consent from the patient or their legal guardians.

Treatment

Patients with OS and ES received neoadjuvant chemotherapy and post-operative chemotherapy; patients with UDPS received routine post-operative chemotherapy; patients with CS and AB underwent only surgical treatment. The resection margin was determined using enhanced MRI images; intraoperative frozen-section biopsy was performed to confirm tumor negativity of margins of the extracted bone. A 3D-printed osteotomy guide plate was used in some patients (Figure 1).

We performed gradient rewarming of cryopreserved segmental bone allografts (Osteolink, Hubei, China) preoperatively. Allografts were successively immersed in sterilized water followed by in hydrogen peroxide for 30 and 15 min, respectively, then rinse thoroughly with sterilized water to remove residual bone marrow and to reduce the immunogenicity. The isometric bone allograft for reconstruction was obtained according to bone defect length

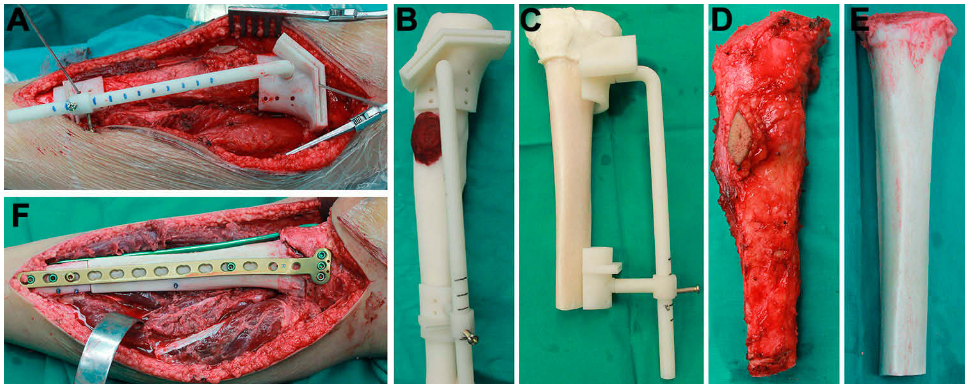

Figure 1 Osteosarcoma of middle tibia operated using a 3D-printed osteotomy guide plate-assisted osteotomy procedure. (**A**) The osteotomy guide plate was placed at the position of osteotomy and fixed with a Kirschner wire. (**B**) The 1:1 bone model and osteotomy guide plate (the red coloring denotes lesions). (**C**) The allograft was osteotomized with another guide plate to achieve accurate matching. (**D, E**) The host (malignant) bone and allograft bone surfaces were osteotomized accordingly. (**F**) The allograft and host junctional surfaces have been matched to the maximum extent.

following tumor resection (Figure 1B and C), and osteotomy interfaces at the host–donor junctions matched well (Figure 1F). The patients fixed with intramedullary nails expanded the marrow of the allograft, while the patients fixed with double steel plates injected with bone cement to strengthen the allograft. In five patients, we prepared two sets of identical osteotomy guide plates by 3D printing to ensure the accurate matching of host–donor junctions, one set for tumor osteotomy and the other for allograft osteotomy (Figure 1A and C). In our opinion, the coincidence area between the allograft and the host is more than 90% of the cross-section of the allograft, which is an accurate match. The shape and size of the tumor bone and allograft intercepted by the guide plate are almost similar (Figure 1D and E). Thereafter, allograft fixation and soft-tissue reconstruction were performed. Allografts were fixed using intramedullary nail (Stryker, Michigan, USA), a double plate (Stryker, Michigan, USA), and an intramedullary nail and plate combination in 2, 5, and 10 patients, respectively. Soft-tissue reconstruction via transposition of muscle (eg, sartorius and the medial head of gastrocnemius) flaps for good tissue coverage of allografts in situ.

Prophylactic use of antibiotics for 7 days and a negative pressure drain were placed in situ until the drainage volume decreased to <10 mL/day. The operated limb was fixed with an external gypsum cast for 4 weeks. Patients were started on isometric muscle exercises

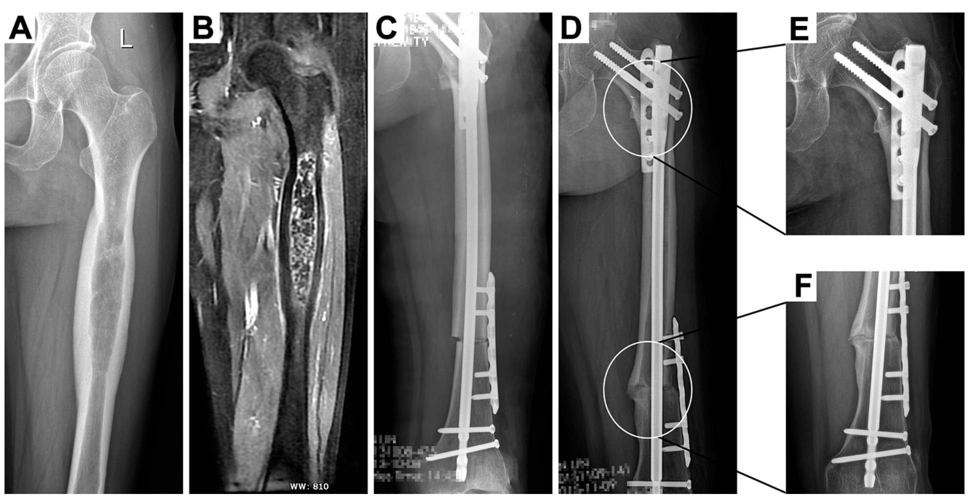

Figure 2 Chondrosarcoma of middle femur. (**A, B**) The lesion is located in the middle part of femur, with calcification shadow and reaction area in medulla. (**C**) Reconstruction of bone defect with intercalary allograft and compression fixation with intramedullary nail and compression plate. (**D**–**F**) 23 months postoperatively, the host–donor bone interface had healed completely.

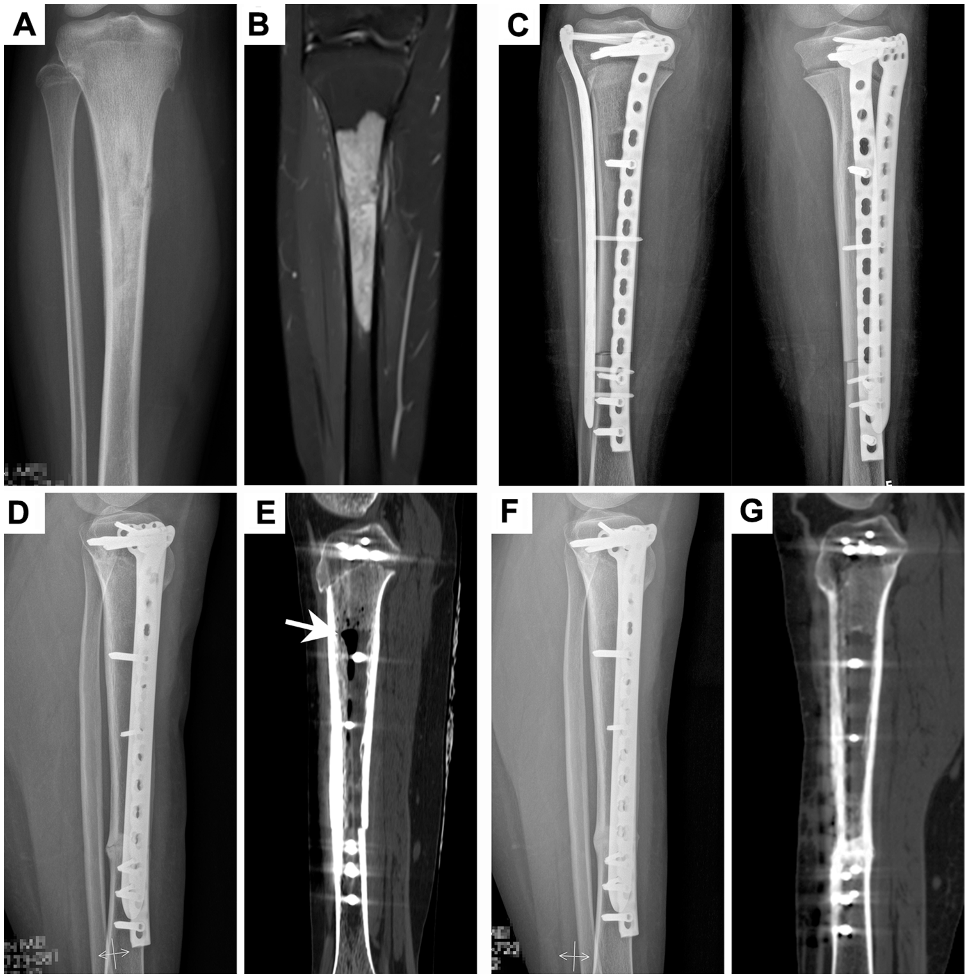

Figure 3 Images of patients with the precise matching of bone host–donor interface. (**A**) Anteroposterior radiographs showed bone destruction in the right tibia and obvious periosteal reaction. (**B**) T1-weighted lipid suppressing enhanced magnetic resonance image used to confirm the size of the lesion. (**C**) Three months after segmental resection and allogenic bone reconstruction. (**D, E**) Lateral radiograph and sagittal computed tomography scan at 6 months after surgery showing initiation of healing of the bone host–donor interface, with very low-density cavities seen in the medullary cavity of the allograft (white arrow indicates the cavity). (**F, G**) Image taken 9 months after surgery, shows a completely healed bone host–donor interface, with an increase in the intramedullary density of the allograft as compared to that of 3 months ago.

immediately after the operation, and flexion and extension exercises of adjacent joints were initiated on cast removal. Patients were allowed non-weight-bearing ambulation after eight postoperative weeks but not partial weight-bearing until there was radiological evidence of graft incorporation, which usually occurred >3 months postoperatively.

Follow-Up and Evaluation

Follow-up radiographs were obtained at 6 and 12 weeks post-surgery and then at every 3-month intervals for the first 2 years, every 6 months for the next 3 years, and annually thereafter. Follow-up included physical examination, chest CT, and X-ray of the operated site. Tumor recurrence was suspected in case of the resurgence of clinical symptoms or on abnormality detection on plain radiographs. Allograft union was evaluated using ISOLS scoring system.[18] At the final follow-up, bone union was defined by an ISOLS score >30, while non-union was either defined as host–donor interface nonunion detected radiologically, or ISOLS score <30. The functional outcome was assessed using the MSTS scoring system.[19]

Statistical Analysis

The data were analyzed using SPSS version 20 (SPSS Inc., Chicago, Illinois). The measurement data are expressed as mean ± standard deviation. The interface matching, complications and other counting data were expressed by specific values. The follow-up data were analyzed by paired *T*-test, independent-samples *T*-test and Chi-square test; P-value<0.05 was considered statistically significant.

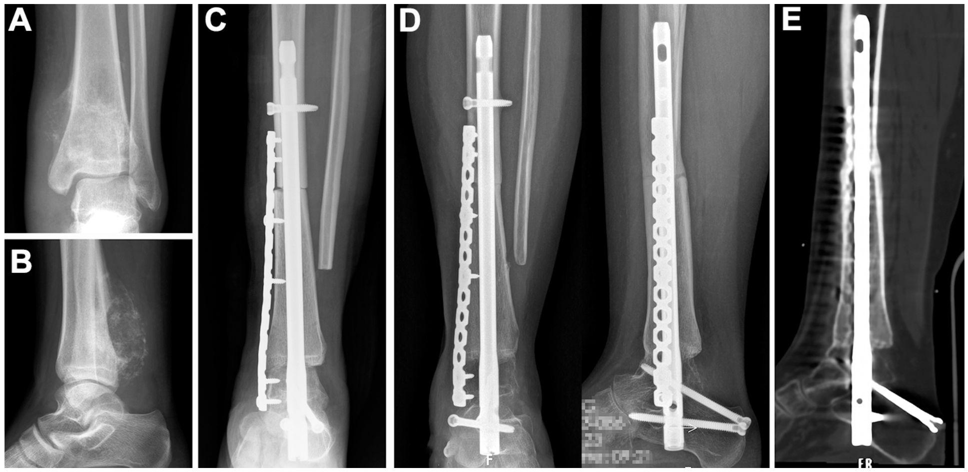

Figure 4 Preoperative and postoperative imaging of osteosarcoma of the distal tibia. (**A, B**) Anteroposterior and lateral radiographs of distal tibia reveal a distinct area of bone destruction and osteogenic changes in the lesion. (**C**) Anteroposterior radiographic image taken 2 weeks after performing segmental resection, allogenic bone reconstruction, and ankle joint fusion. (**D, E**) Anteroposterior and lateral radiographs taken at 12 months after surgery showing a partially healed host–donor diaphyseal interface with a completely healed metaphyseal junction. Sagittal computed tomography also confirmed that the epiphyseal host–donor interface had indeed healed completely, while the diaphysis was only partially healed.

Results

We performed intercalary allograft reconstruction of the femoral and tibial shafts in seven and four patients (Figures 2 and 3), respectively; another four patients underwent distal tibial reconstruction with ankle arthrodesis (Figure 4). The average allogenic bone graft length used in this group was 17 (range: 12.5–24.5) cm. No procedure-related operative complications were noted. The mean follow-up time was 49.8 months (26 to 78).

Oncology Prognosis

Up to the last follow-up, 13 cases survived without tumors, 4 cases survived with tumors and was treated with oral-targeted drugs for lung metastasis, and 1 case died of lung metastasis of osteosarcoma. Among them, two cases received amputation because of local recurrence after bone healing.

Healing of Host–Donor Junctions

Among the 34 host–donor junctions of 17 cases, 32 junctions had bone healing, of which five cases had accurate osteotomy with a 3D printing guide plate (Figure 2). The healing time was 6–22 months, with an average of 12.1 months. The healing time of metaphysis (9.1 mon) was significantly shorter than that of bone shaft (16.3 mon) ($P < 0.05$) (Table 1) and the use of osteotomy guide plate can achieve accurate matching to shorten the healing time, indicating that the more prone the metaphysis to bone healing (Figure 4). Host–donor junctions in two patients showed nonunion. The probability of nonunion was 6.77% in patients receiving chemotherapy (Table 2).

Functional Prognosis and Complications

Neither infection nor allograft fracture occurred in this group. Although four patients developed postoperative immune response, mainly manifested as fever and wound swelling of unknown cause, the symptoms abated with low-dose dexamethasone administration. There was no loosening or breaking of internal fixators, and limb salvage rate was 94.1% at the end of the final follow-up. Postoperative limb function according to the MSTS system averaged 24.2±5.3. Excellent and good ISOLS scores were achieved in 76.5% of patients (Table 1).

Discussion

The reconstruction methods for diaphyseal defects after primary malignant bone tumors resection include artificial prosthesis replacement,[2] autogenous bone transplantation,[20,21] allogeneic bone transplantation,[9,22,23] masquelet technique,[24] bone lengthening,[25] autogenous devitalized bone reimplantation,[5] autogenous fibula composite allogeneic bone transplantation,[26] and so on. Rates and durations of survival, impact on the next steps of treatment, and possible complications should be considered while choosing the reconstruction method. Sometimes the tumors are located in the diaphysis, and the residual bone after segmental resection cannot be effectively fixed by the artificial prosthesis, so amputation is necessary. Allogeneic bone is a bone defect repair material

Table 1 Summary Data of Patient Information

General Information		Mean	SD	
Age		24.9	12.5	
Allograft length (cm)		17.0	3.1	
Duration of follow-up (month)		49.8	15.7	
MSTS score		24.2	5.3	
Potential factors		**Number**	**Percentage**	**P-value**
Gender	M	9	53%	
	F	8	47%	
Anatomical location	Femur shaft	8	47.1%	
	Tibial shaft	4	23.5%	
	Distal tibia	5	29.4%	
Complication	Relapse	2	11.8%	
	Delayed wound healing	2	11.8%	
	Metastasis	3	17.6%	
	Nonunion	2	11.8%	
	Immune response	4	23.5%	
Healing time	Diaphysis	16.3	3.3	<0.001
	Metaphysis	9.1	1.8	
ISOLS score	Excellent	8	47.1%	
	Good	5	29.4%	
	Poor	4	23.5%	

Abbreviations: MSTS, Musculoskeletal Tumour Society scoring system; ISOLS, International Society of Limb Salvage scoring system.

with good histocompatibility, high mechanical stability, strong bone conduction, and excellent osteoinductive ability, which can last a lifetime once it survives. It is an excellent choice in the treatment of limb salvage and nonunion.[4,9,27–31] Rollo G et al.[28–31] reported that the use of allograft in the treatment of aseptic nonunion has achieved good results, and it also has significant advantages in fracture revision surgery. However, its application has been limited because of potential complications and controversial prognosis.[10,14,16,32]

Segmental allograft healing implies host–donor junction healing. Large segmental allografts cannot be completely transformed into host bone, which relies on the callus formed and induced osteogenesis by the host to gradually completes the creeping substitution process.[11,13,33] The reported rate of nonunion in large bone allograft reconstruction is 9%~63%, with an average of 34%.[34] Aponte TL[35] reported a 13% incidence rate of nonunion after interfemoral allograft transplantation with diaphyseal junction showing higher nonunion than metaphyseal junction. Other studies reported nonunion incidence rates of 40% after allogenic bone transplantation for bone defect repair and simple intramedullary nailing or using >10 cm bone grafts increases the nonunion risk.[11,15] A comparative analysis of allogenic and autogenous bone transplantation for repairing distal tibial bone defects showed higher complications of allogenic bone transplantation, with nonunion incidence reaching 27%.[22] Muscolo DL et al[1] used allogenic bone grafts to repair tibial and femoral interpositional bone defects and found that 37% patients needed reoperation because of complications, while 41% experienced nonunion. Although vascularized fibula and massive bone allograft can effectively accelerate bone healing,[36] the extension of the operation time, the inability to use intramedullary nail fixation and the influence of chemotherapy on blood vessels limit its application in our study. In this study, the overall healing rate of 88.2%, and the average healing time was 12.1 months, which was shorter than the previous reports.[11] The healing time of metaphysis was significantly shorter than that of bone shaft and the use of osteotomy guide plate can achieve precise matching to shorten the healing time. It is suggested that the successful rate of repairing bone defect with large bone allograft in lower limbs is higher, which may be related to more stress stimulation in lower limbs, and the accurate matching of graft and host junctional surfaces increases the contact area leading to satisfactory prognosis.

3D printing osteotomy guide plate is an excellent assistant for precise osteotomy, which can design accurate osteotomy according to the preoperative design and achieve a perfect match with the allograft. As the shaft is rigidity and incompressible, we usually use wire saw, pendulum saw, ultrasonic scalpel and other methods to cut off or meticulous treat the allograft. But in the actual operation process, the subjective error is inevitable. When the force line seems to be correct, it usually appears that the allograft has good contact with the host bone, but in fact, most of the surfaces are not in contact with each other, only some points are well matched, and there are still small gaps, which is no problem for simple fracture healing. However, for large-segment allograft, these gaps may lead to an imbalance of stress

Table 2 Analysis of Related Factors of Bone Healing

Potential Factors		Total Number	Number of Nonunions	Percentage	P-value
Interface position	Diaphysis	17	2	11.76%	<0.05
	Metaphysis	17	0	0.00%	
Matching degree	Precise	5	0	0	<0.05
	Rough	12	2	16.67%	
Method of fixation	IMN	2	2	100%	<0.05
	DP	5	0	0	
	INCP	10	0	0	
Chemotherapy	Y	15	1	6.67%	>0.05
	N	2	1	50%	

Abbreviations: IMN, intramedullary nail; DP, double plate; INCP, intramedullary nail-combined plate.

stimulation and affect healing. In order to solve this problem, we carefully selected the grafts according to the length and diameter of the resected bone, and the same size osteotomy guide plate was used to cut the transplanted bone. Surprisingly, the osteotomy surface matched very well. This method is very simple, but the exact result needs to be confirmed by further large samples.

In this study, one patient underwent amputation due to recurrence, but imaging showed that the host–donor bone interface had healed. Histopathological analysis of host–donor junction (post-amputation) showed the formation of complete osseous junctions and many new haversian systems at the host–donor interface (Figure 5). The number of cells in the lacunae and bone mass at host bone junction were greater than that at the allograft (Figure 5A). Immunohistochemical results with CD31 staining revealed several blood vessels in the lacunae of the graft–host interface and the host bone but none in the allograft (Figure 5B). These findings indicated that bone healing occurred mainly at the interface, while the vascularization of allograft was difficult to achieve (Figure 5). Thus, once graft–host

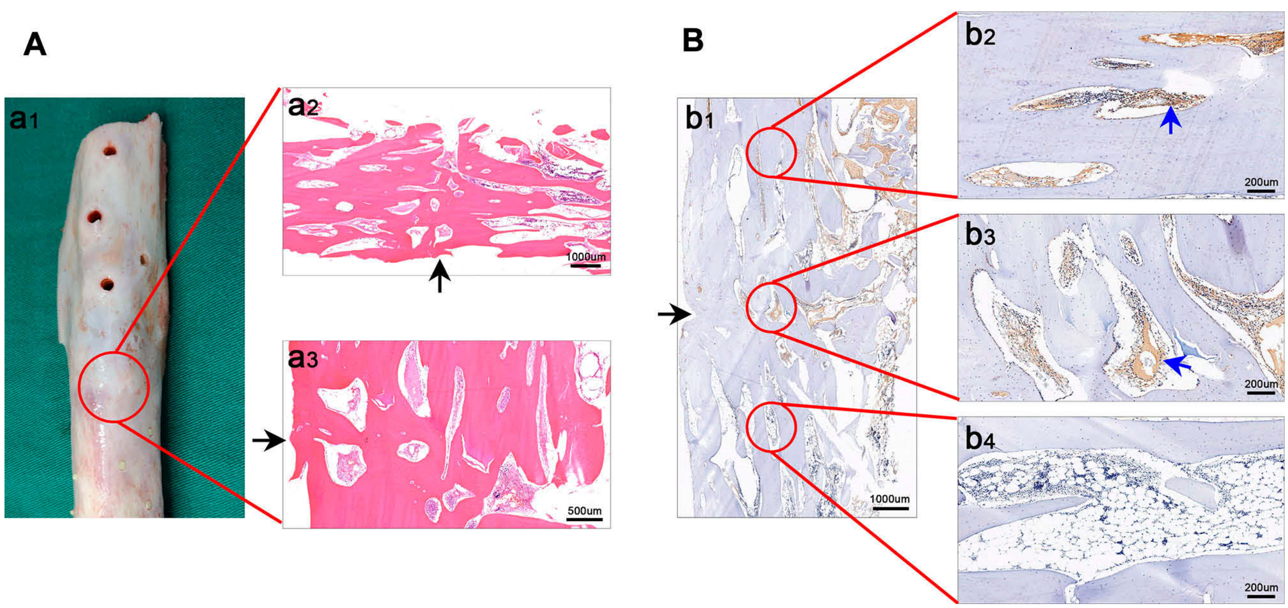

Figure 5 Histopathological characteristics of the bone host–donor interface (specimens of patients amputated due to recurrence). (**A1**) The specimen of amputated patients, with images of the host bone at the top and of the allograft bone at the bottom, shows that the host–donor interface has completely healed. (**A2, A3**) Microscopic images of the bone host–donor interface after hematoxylin-eosin staining show complete osseous junctions and many new Haversian systems. The number of cells in bone lacunae and bone mass at the host bone are greater than those at the allograft (a1 is a 15× magnified image of the host–donor interface, with the host bone image on the left and the graft bone image on the right. a3 is a 35× magnified image of the host–donor interface. The black arrow points to the host–donor interface). (**B1**–**B4**) Immunohistochemical staining of CD31 shows many vessels in the bone lacunae of the host–donor interface and host bone, while no blood vessels can be seen in the allograft. This indicates that bone healing has occurred mainly at the host–donor interface, and that vascularization of allograft was difficult to achieve (the black arrow indicates the host–donor interface, the blue arrow indicates the positive region of CD31, which is a specific marker of vascular endothelial cells). The allograft lacuna shows many dead cells with no angiogenesis, and only the cortical surface of allograft shows signs of being replaced by the creeping host bone tissue.

junction has healed, local bone strength is restored and increases over time. Allografts can last a lifetime, which is their biggest advantage as compared to prosthesis replacement.

The complications of intercalary allograft transplantation are also troubling. Allograft fracture,[10,16,37-39] deep infection and immune response have been reported in previous studies, and the prognosis is not optimistic. Allograft fractures are difficult to heal because of their lack of biological activity and revision surgery is often inevitable. Fortunately, there were no allograft fractures in this study. The application of high-strength internal fixation may be a critical factor in preventing allograft fractures, which theoretically should be the standard procedure used for segmental allograft transplantation. Infection after allograft transplantation is a catastrophic complication. Removal of the allograft or amputation, if necessary, is often the only option.[14,26] Studies[14,40] have shown that radiotherapy and chemotherapy may increase the probability of postoperative infection. Surprisingly, although 88% (15/17) of our patients received chemotherapy, no postoperative infection occurred in this group, with only 2 patients showing delayed wound healing, possibly due to good soft-tissue coverage of the allogenic bone and adequate drainage of the wound postoperatively.

Our findings indicate the obvious advantages of using intercalary allograft for lower extremity diaphyseal defect reconstruction after tumor resection, but some details must be strictly grasped: ① tumor resection must be thorough to achieve good oncological prognosis; ② long term and absolute stable internal fixation is the guarantee of successful allograft transplantation; ③ increased osteotomy surface contact at host–donor junctions to the maximum extent possible and compressed contact surfaces effectively accelerate bone healing and prevent bone resorption; ④ adequate soft-tissue coverage to provide a good osteoinductive environment and reduce the risk of infection; ⑤precise preparation of allograft and adequate drainage facilitated postoperatively are also important.

Our study has certain limitations. First, the sample size was small to determine the incidence of complications accurately. Second, this was a retrospective study, and direct or randomized comparisons were not performed. Lastly, follow-up of some patients was inadequate to assess long-term complications. We hereby analyze the results of the application of this technique in lower limbs, hoping to provide help for clinical treatment. We also look forward to large sample, multi-center, prospective studies to obtain more accurate results.

Conclusion

Intercalary allograft transplantation is effective for diaphyseal defect following post-tumor resection in the lower extremity. Good bone healing after allograft reconstruction is achieved with stable internal fixation and perfectly matched host–donor interfaces. Optimizing the details of the treatment can effectively reduce the occurrence of postoperative complications and achieve a better prognosis.

Abbreviations

CT, computed tomography; MRI, magnetic resonance imaging; ISOLS, International Society of Limb Salvage; MSTS, Musculoskeletal Tumor Society; OS, osteosarcoma; CS, chondrosarcoma; AB, ameloblastoma; UDPS, undifferentiated pleomorphic sarcoma; ES, Ewing sarcoma.

Ethical Review Committee Statement

This study has been approved by the Research Ethics Committee of Xiangya Hospital.

Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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