Orthopaedic Surgery

CASE REPORT

# 3D Customized Biological Tibial Intramedullary Nail Fixation for the Treatment of Fracture after Massive Allograft Bone Transplantation of Tibial Osteosarcoma: A Case Report

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Allograft bone fractures are critical complications in massive allograft bone transplantations. There are limited studies available on the application of 3D printing for massive allograft bone transplantation complications, and no related reports on the treatment of an allograft bone fracture with a complete biological intramedullary nail. A complex case of allograft bone fracture after massive bone transplantation for a right tibial osteosarcoma was treated with fixation of an individualized 3D printed biological tibial intramedullary nail. Prior to the operation, the intramedullary nail was designed and printed based on the results of computed tomography examination of the affected limb, and the surface of the intramedullary nail was treated with a hydroxyapatite coating. Intraoperatively, the intramedullary nail was implanted according to the preoperative 3D design plan. The intraoperative and postoperative examinations showed that the 3D printed intramedullary nail achieved good matching between the implant and the medullary cavity, and the biological coating integrated well with surrounding bone. The follow-up results 44 months postoperatively showed that the patient was satisfied with the surgical results, where his ankle function met his daily needs, and the Musculoskeletal Tumor Society score was 24. 3D printing tibial intramedullary nail fixation can be successful in the treatment of allograft bone fractures and should be considered as a treatment of choice. In this case, the intramedullary nail matched the surrounding bone well, had good osseointegration, and the patient regained basic function.

**Key words:** Allografts; Case report; Fracture; Intramedullary; Osseointegration; Osteosarcoma

## Introduction

Allograft bones can be successfully used for the repair and reconstruction of both segmental bone defects in the major limbs and limb salvage treatment after bone tumor resection.[1,2] However, there remain several unsolved challenges associated with allograft bone transplantation, specifically massive allograft bone transplantation, such as immune rejection, infection, bone resorption, bone nonunion, and allograft bone fracture. The surgical failure rate caused by infection, fracture, and nonunion was reported to be 25% in patients who underwent large allograft bone transplantation.[3–5] The treatment plan for these complications differs according to lesion site, complication type, surgeon's experience, and technical conditions. Although there is always a risk of re-fracture, the traditional method used for allograft bone fractures remains re-fixation.[4,5]

We report a case where we used an individualized three-dimensional (3D) printed biological tibial intramedullary nail to treat an allograft bone fracture in a complex case of massive allograft bone nonunion in a patient with tibial osteosarcoma. The decision to use this prosthesis was based on our successful experience with osseointegration and clinical outcomes of biological prostheses. The follow-up period of this case was over 44 months with a good final

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Received 2 November 2021; accepted 30 March 2022

clinical effect. To the best of our knowledge this is the first report to date that describes the successful use of a 3D customized biological tibial intramedullary nail to treat an allograft bone fracture.

Conventional implants often cannot meet the specific requirements of allograft bone fractures; however, 3D customized designs can make up for this shortcoming, provide individual choices for the treatment of allograft bone fractures, and better meet the needs of patients and clinicians. The good osseointegration and fixation effect of the biological intramedullary nail procedure described here provides an example of a successful alternative for the treatment of allograft bone fractures.

## Case Presentation

### *Clinical Data*

#### *Diagnosis and Preoperative Chemotherapy*

A 16-year-old male patient who presented with pain and swelling of the lower part of his right leg was admitted to our hospital in February 2011. Radiography revealed a bone abnormality in the right distal tibia. Upon examination by computed tomography (CT), magnetic resonance imaging (MRI), emission computed tomography (ECT), and pathological biopsy, the patient was diagnosed with an osteosarcoma. The tumor involved the medullary cavity, bone cortex, and posterior soft tissue of the distal tibia and spanned from 15–145 mm above the ankle joint toward the proximal tibia. There was limited soft tissue involvement in the anterior lower segment of the posterior tibial muscle that did not involve the superficial layer of the muscle (Fig. 1). The treatment regimen was three cycles of preoperative neoadjuvant chemotherapy (epirubicin 80 mg/m$^2$ + methotrexate 10 g/m$^2$). Re-evaluation 1 month after neoadjuvant chemotherapy showed significant analgesic relief, soft tissue hardening at the tumor site, and that the chemotherapy was clinically effective. The patient was referred to undergo limb salvage treatment.

#### *Tumor Resection, Large Segmental Allograft Bone Transplantation, and Fixation*

The first operation was performed on June 21, 2011 after three courses of neoadjuvant chemotherapy. The surgical procedure involved segmental resection of the right tibial osteosarcoma, massive allogeneic bone transplantation, artificial bone grafting, plate and screw internal fixation, and tibiotalar joint fusion. An anterior tibial incision was used for the extended resection of the tumor, whereby the resection length was 175 mm from the ankle point (30 mm from the proximal end of the osteotomy to the upper edge of the tumor). Furthermore, 5 mm of the talus (upper part) was removed and the soft tissue associated with the distal posterior tibialis muscle was completely resected. The allograft bone (from Sichuan bone bank) was inactivated by deep cryopreservation at −80°C. The allograft bone was trimmed to 180 mm and fixed between the talus and the proximal tibia using a plate and screws (16 holes, LC-DCP, Shandong WeiGao Medical equipment Company, Weihai, Shandong, China; Fig. 2). The ankle joint portion of the allograft was perforated to provide a ligament attachment point. The artificial bone graft (nano-hydroxyapatite/polyamide-66 composite bone filling material, Sichuan Guona Science and Technology, Chengdu, Sichuan, China) was placed on the interface between the allograft and autogenous bone. The patient performed postoperative functional exercise according to the doctor's instructions. Regular follow-ups took place and chemotherapy continued for four courses postoperatively.

#### *Treatment of Massive Allograft Bone Nonunion and Fracture*

The patient was able to mobilize independently with resolved symptoms after 3 months (October 2011). However, in May 2012 (10 months post-op) he complained of ankle pain and discomfort. Re-examination by x-ray on

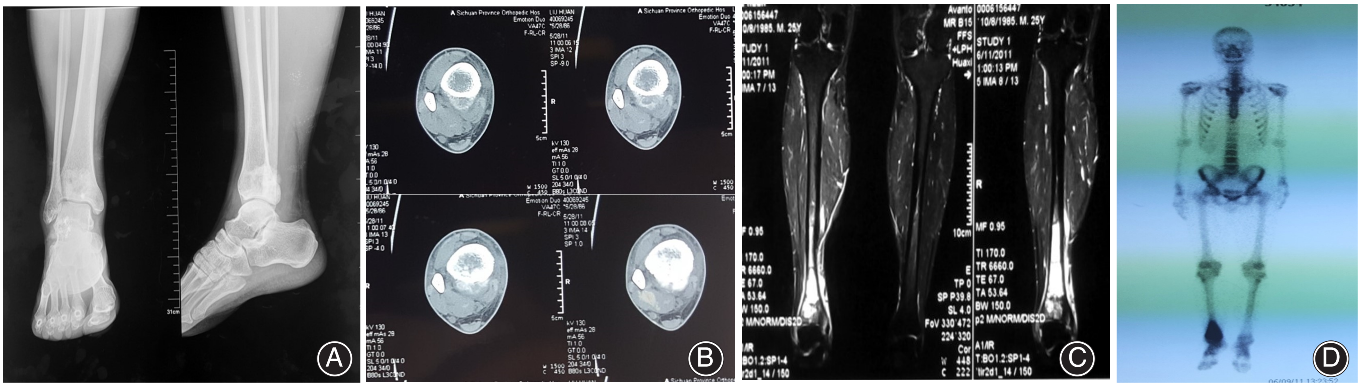


**Fig. 1** Preoperative imaging data. (A) X-ray image (anteroposterior and lateral views) shows a bone abnormality in the distal right tibia. (B) Computed tomography of the distal right leg shows lesions of the bone and soft tissue. (C) Magnetic resonance imaging shows an abnormally signal in and around the distal right tibia. (D) Emission computed tomography shows abnormal concentration of radionucleotides in the right tibia

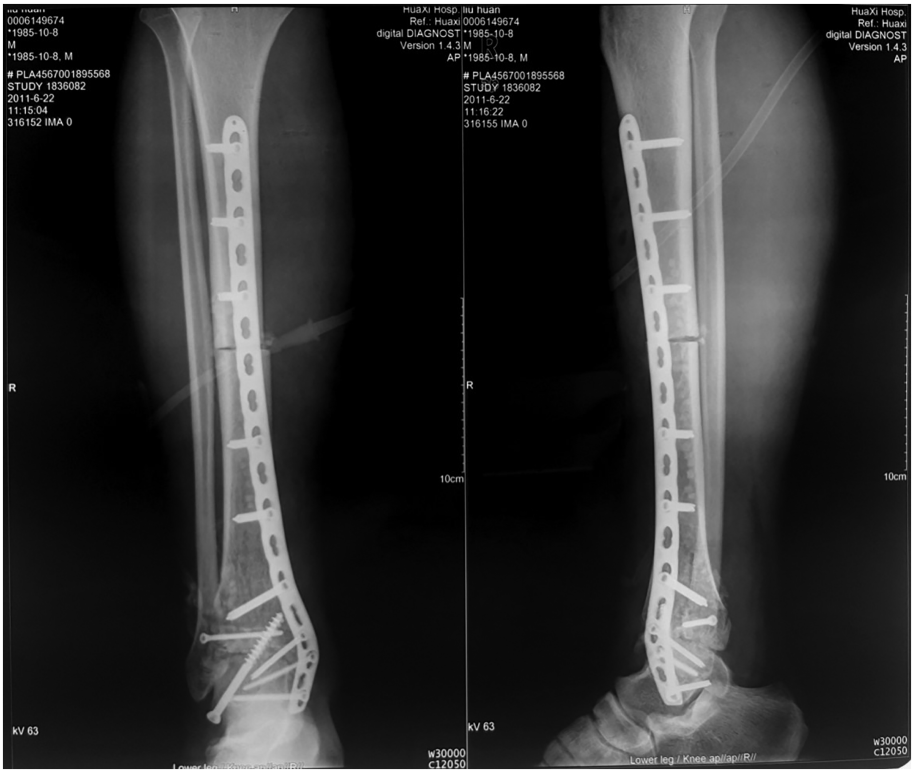


**Fig. 2** X-ray image (anteroposterior and lateral views) on the first postoperative day after the first operation

different follow-up visits showed nonunion at the distal host-allograft interface and fracture of the internal fixator (Fig. 3). In July 2012 (12 months post-op) the patient underwent an autogenous iliac bone graft and fusion of the right tibiotalar joint. Pathological examination was performed and no tumor recurrence was found. The patient returned to independent functional living after 2 months of protective functional exercise. Seventeen months after the first fixation (January, 2013), a loose screw and an allograft bone fracture was found on X-ray imaging (Fig. 3). The patient underwent a smaller third operation for the removal of the loose screw in May, 2014. Unfortunately, 5 months after the third operation (October, 2014) the patient complained of pain that affected his activities of daily life. Radiography revealed regression of the allograft bone fracture (Fig. 3).

After the occurrence of the allograft bone fracture, the patient was apprehensive of a new operation and requested a conservative treatment. The physician prescribed right lower limb restricted weight-bearing and a conservative treatment for 18 months. However, the pain in the affected limb was not relieved when walking. The allogeneic bone fracture showed no signs of healing on X-ray imaging (Fig. 4). In July 2016, at the patient's request, the doctor removed the internal fixator, and mechanical stimulation was used to promote the growth of the allograft bone. However, there was no bone growth after 10 months of treatment (Fig. 4). There was a fatigue fracture at the lower fibula and varus deformity of the lower extremities (Fig. 4).

*Design and Implementation of a 3D Customized Biological Tibial Intramedullary Nail Fixation for Allograft Bone Fracture*

Doctors examined the affected limb with three-dimensional CT (3D-CT) and used the findings to design and prepare a 3D-customized biological tibial intramedullary nail (based on a biomechanical study that confirmed the casting strength would be more suitable for the patient) that was used for retrograde penetration from the calcaneus into the proximal end of the tibia.

The intramedullary nail was designed by the operator according to the patient's bone medullary cavity and length and molded by Chunli Co. Ltd. (Beijing, China); the surface was sprayed with hydroxyapatite (two 0.5–1.0-mm layers; Chunli) that met the standard requirements of GB23101.2–2008. The fixed guide plate required was also designed by 3D customization and the nail-holding equipment was also provided by Chunli (Fig. 5).

The chief surgeon who designed the intramedullary nail system performed the operation according to the preoperative plan. The procedure of operation is described in Fig. 5. First, the site of the allograft bone fracture was exposed using an anterior incision and the sclerotic bone was resected. After correcting the force line of the lower limb, an opening was made at the bottom of the foot to expand the medulla to match the diameter of the intramedullary nail from the calcaneus to the proximal tibia. The nail holder was used to retrograde the intramedullary nail into the proximal tibia from the opening of the calcaneus,

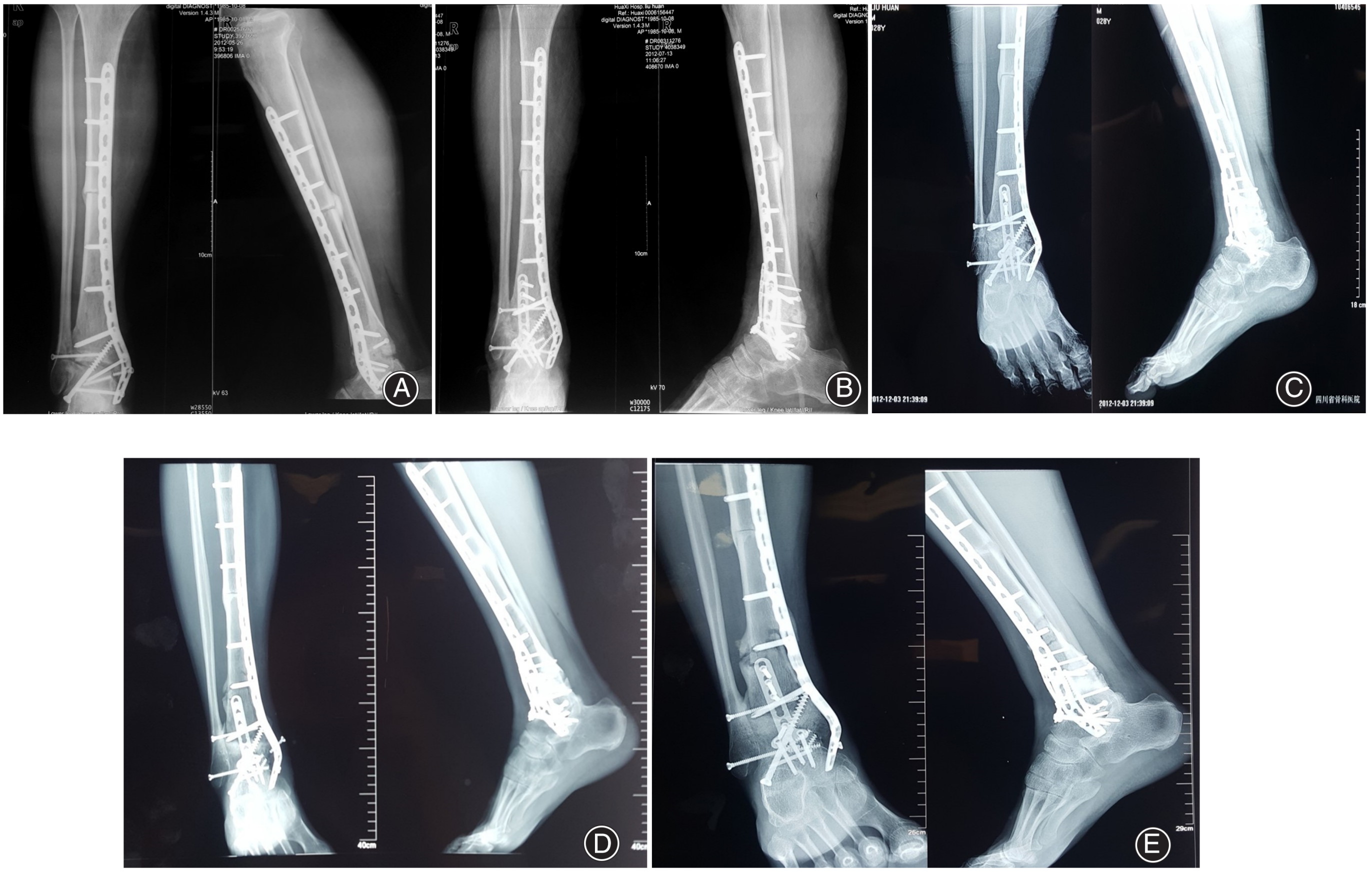


**Fig. 3** Follow-up X-ray image (anteroposterior and lateral views) before and after the second operation. (A) Eleven months after the first operation: bone union occurs at the proximal host-allograft interface but there is no union at the distal. (B) Image of the first day after the second operation shows the internal implant that was used to strengthen the fixation of the distal host-allograft interface with the grafted bone. (C) Five months after the second operation, there is bone healing at the distal interface. (D) Seventeen months after the second operation, some screws are loose, bone healing of the distal host-allograft interface is complete, and a fracture line can be seen in the middle of the allograft bone. (E) Five months after the third operation, there is aggravation of the allograft bone fracture


**Fig. 4** X-ray images (anteroposterior and lateral views) of pre- and post-operative of removal the internal fixator. (A) Twelve months after the third operation, the fracture line is clear with no healing. (B) X-ray image (anteroposterior and lateral views) taken immediately after the fourth operation were internal implants are removed. (C) Ten months after the fourth operation, allograft bone fracture is aggravated, accompanied by fatigue fracture of the lower fibula and varus deformity of the lower extremities


**Fig. 5** (A–D) Display the three-dimensional analysis and the design of the personalized intramedullary nail. (E) Biological tibial intramedullary nail system and supporting equipment: on the left is the nail holder, in the middle is the biological tibial intramedullary nail, and on the right is the guide plate. (F) Operation using the biological tibial intramedullary nail system in the treatment of the allogeneic bone fracture

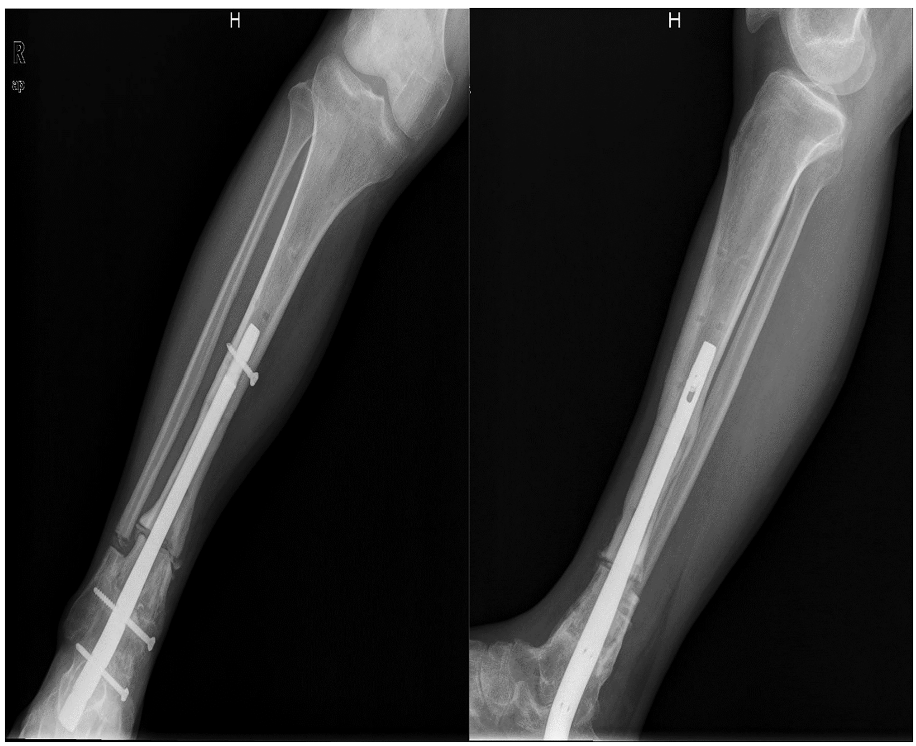


**Fig. 6** X-ray image (anteroposterior and lateral views)- after the fifth operation

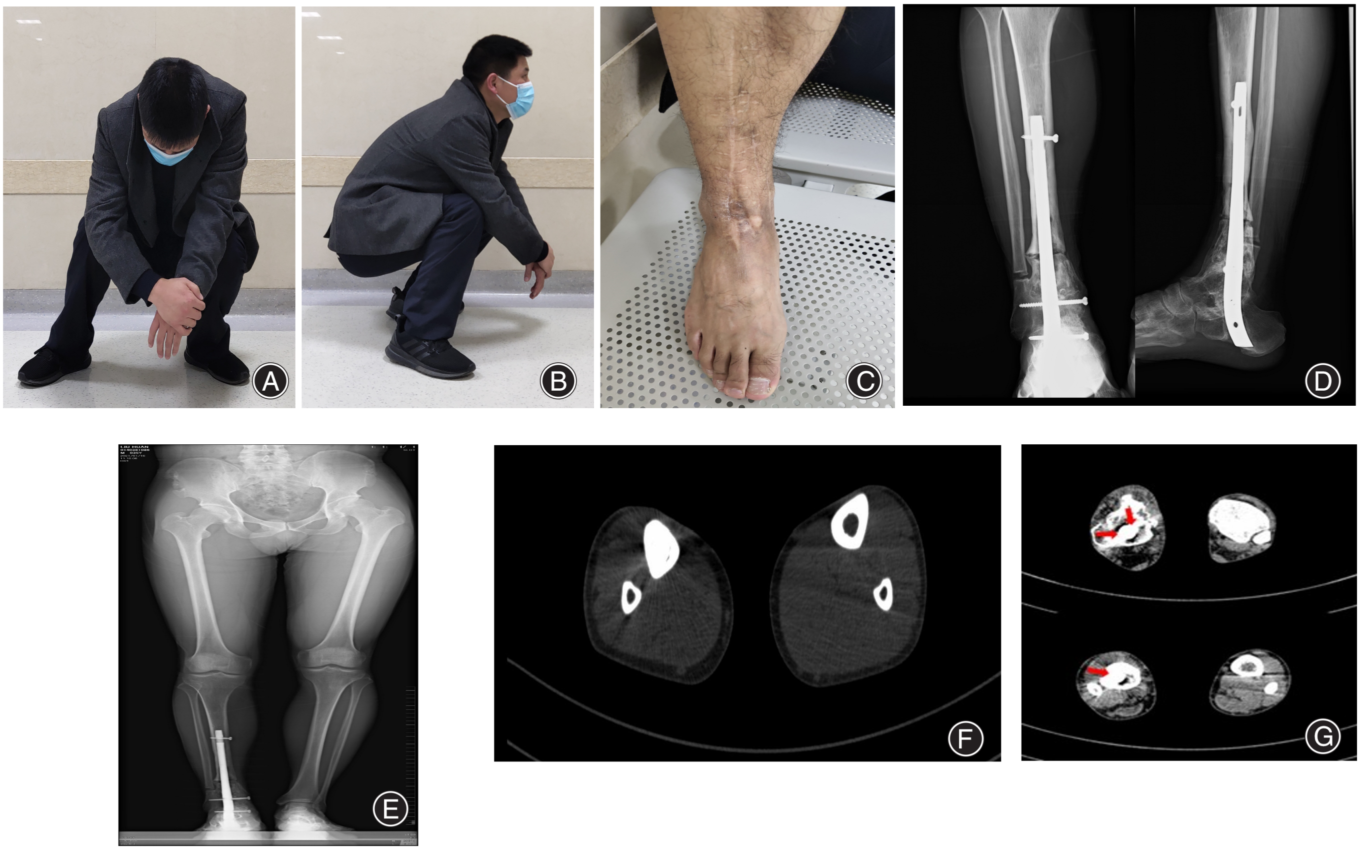

**Fig. 7** Follow-up results 44 months after the fifth operation (customized nail insertion). (A–B) Function of the right ankle joint. (C) Healing of the wound. (D) X-ray (anteroposterior and lateral views) image 44 months after the fifth operation shows callus formation at the broken epiphysis, but the fracture line still exists, and the intramedullary nail is closely combined with the bone. (E) X-ray image (anteroposterior view) in the standing position of both lower limbs shows that the limbs are equal in length, and that the force line is intact, without valgus deformity. (F) Postoperative computed tomography (CT) scan shows that the 3D customized intramedullary nail system matched the tibial bone marrow cavity. (G) Postoperative CT scan shows that the 3D customized biological intramedullary nail system integrated well with the host bone (red arrow)

and the locking screw was inserted into the distal and proximal tibia using the 3D printed guide plate. The fracture was filled with autogenous iliac bone graft. No surgical complications were experienced and the wound healed well. The postoperative X-ray image showed that the position of the internal fixator was correctly placed as planned (Fig. 6). The patient began to walk without assistance or pain after the wound had healed. The patient was non-compliant with the follow-up schedule prescribed by the doctor. He reported that the postoperative limb pain had resolved and that there was no obvious discomfort, and therefore he did not attend the follow-up appointments. However, we followed up on the results 44 months after the last operation and found him to be independent in all activities of daily living, with normal weightbearing and mobility. However, he did have limited movement of the ankle joint and had difficulty with squatting. The patient was satisfied with the results of the operation, which had a Musculoskeletal Tumor Society score of 24. The final X-ray showed a small amount of callus formation at the fracture end of the allograft bone and fibula. Whilst the fracture did not heal completely, the intramedullary nail had closely adhered to the surrounding bone. A CT scan showed that the intramedullary nail system matched well with the tibial bone marrow cavity, and the biomaterials on the surface of the intramedullary nail were well integrated with the host bone (Fig. 7).

## Discussion

### *Selection of Treatment for Large Bone Defect after Resection of Limb Bone Tumor*

There are several methods to perform limb salvage for the treatment of segmental bone defects caused by malignant bone tumors, such as prosthesis reconstruction, distraction osteogenesis, and biological reconstruction, each with their own advantages and disadvantages.[6] For large bone defects that do not involve the articular surface, distraction osteogenesis (Ilizarov method) of bone regulation has good results.[7] Rollo *et al.* confirmed that the Ilizarov method combined with osteogenic factors, such as teriparatide and platelet rich plasma, can greatly improve the osteogenic efficiency.[8,9] Nevertheless, Tsuchiya *et al.*[10] stated that this method should be reserved for segmental defects with a length <15 cm, making the technique inappropriate for larger bone defects. Moreover, patients may tolerate the Ilizarov frame poorly. For patients where the removal of the distal tibia articular surface is required, prosthesis reconstruction and distraction osteogenesis have limitations, and biological reconstruction would be the first choice. The commonly used methods of biological reconstruction are inactivated autogenous bone replantation, large segment allograft bone transplantation, and compound reconstruction of the vascular pedicled fibula graft. Autogenous bone grafting (vascularized fibular autografts) and internal fixation is an advantageous biologic method of reconstruction for the management of nonunion and fracture, however, it may require prolonged non-weight-bearing status to allow for union/graft hypertrophy.[11,12] The advantages of a large segment allograft bone transplantation[13] are that the shape is consistent and it can provide attachment points for the muscle, ligaments, and joint capsule. Due to the use of cryopreservation, the allograft bone maintains its original biomechanical properties, produces bone induction after rewarming, leads to solid biological healing at the epiphysis, and has a better long-term function when compared with that of artificial prostheses.[6,11] Infection and mechanical complications after massive allograft bone transplantation must be considered by orthopedic surgeons.[3,5,6]

The patient in this case report was 16 years old at the time of the hospital visit. After neoadjuvant chemotherapy, successful segmental resection of the right tibial tumor, allograft bone reconstruction, and limb salvage were performed. There was no tumor recurrence or metastasis observed in the 9 years after the operation. We believe that the patient met the standard of clinical cure for osteosarcoma. After tumor segmental resection, a tibiotalar joint fusion was performed, with the talocalcaneal joint preserved, after an allograft bone transplantation of corresponding length. This decision was made after consideration for the importance of weight-bearing and ankle joint function, which was partially functional after the operation.

### *Selection of Treatment for Bone Nonunion and Fracture of Large Segmental Allograft*

Unfortunately, the patient experienced two complications (allograft bone nonunion and fracture) during treatment that took several operations to manage. The incidence of host-allograft interface nonunion ranges from 17%–50% and seems to be higher with the intramedullary nail technique.[14,15] Whilst the proximal allograft bone fused well with the host bone after the first operation, the distal allograft bone did not. The possible reasons for this could be that the allograft bone was too long and the stability of distal fixation with the plate was poor, the associated effects of chemotherapy could have increased the incidence of host-allograft interface nonunion, or the tumor resection led to a lack of sufficient periosteum and poorly vascularized soft tissue. Therefore, to retain the original surgical fixation, bone grafting and plate fixation were successfully performed.

An allograft bone fracture occurred 35 months after the first operation. The possible reasons for the fracture could be that the allograft bone only activated around the area of contact with the host bone and the mechanical strength of the allograft bone was still poor, the plate and screw were loose and the fixation strength was weak, or the fracture occurred at the proximal end of the internal fixator placed during the second operation due to a higher stress concentration.

Many studies have found the incidence of allograft bone fracture to be more likely to occur with the use of a plate than with intramedullary fixation[11,16–19]; furthermore, firm intramedullary fixation has been suggested to significantly reduce the complications during the process of allograft bone healing.[20–26] Fracture risk has been noted to increase in the third postoperative year for allograft bone grafts,[14,21,27,28] which can be accompanied by internal fixation failure. For those without clinical symptoms, conservative observation treatment can be chosen; however, more patients require interventions like allograft replacement, refixation, replacement with prosthetic implants, and insertion of autologous fibula graft with free blood vessels within the allograft. The literature review on the treatment scheme of allograft fracture is shown in Table 1. Longer treatment time, higher revision rate, and amputation, make allograft bone fracture a daunting complication. Gharedaghi *et al.*[19] claimed that the management of allograft bone fractures should be decided based on the surgeon's experience and new treatment methods should be developed. The use of 3D customizing or printing technology to develop individual internal fixators and grafts, combined with biomaterial research and other biological reconstruction methods, can better meet the needs of doctors and patients.[27,29–31] In the case reported here, we designed and prepared a biological intramedullary nail fixation system from the calcaneus to the tibia to treat an allograft bone fracture. To the best of our knowledge, the use of this nail fixation system has not been previously reported. Its advantage is that CT data can accurately determine the medullary cavity size, lesion length, and fixation length for the dimensions of the intramedullary nail that allows for an individualized application of the internal fixation system and implementation of the doctor's treatment plan. The biological coating on the surface of the fixator increases its contact area with the bone and makes it conducive for osseointegration. This procedure is similar to the treatment of bone defects by reconstruction with allograft-prosthetic composites (APCs). In this case, once the three components (fixation system, allograft bone, and host bone) were successfully integrated, better mechanical strength could be obtained and re-fracture prevented. Compared with autologous bone transplantation, 3D

**TABLE 1 Review of the literature**

| Author | Year | Number of Allograft | Rate of Allograft fracture | Treatment of fracture | Outcome |
|---|---|---|---|---|---|
| Albergo *et al.*[20] | 2020 | 71 | 24% | One patient was treated with vascular fibula graft; 11 patients were treated with a new intercalary allograft; Five cases were performed with endo-prosthetic | Nonunion in four patients requiring reconstruction |
| Claudio Giannini1 *et al.*[16] | 2020 | 35 | 25.7% | Four patients were treated with a second intercalary allograft and fixation; three patients with a combination of an autologous fibular graft; two patients were treated with hardware substitution and autologous iliac bone grafting | Two patients chose amputation due to limb salvage failure |
| Aponte-Tinao[21] | 2012 | 83 | 17% | One patient was fixed with another allograft bone; nine patients were replaced with new allograft; four patients were treated with prosthetic replacement | Eight cases failed and needed reoperation |
| Chen *et al.*[22] | 2005 | 14 | 14% | Two patients were treated by fixation using a plate and an autogenous graft from the iliac crest | Both were successful |
| Deijkers *et al.*[23] | 2005 | 35 | 34% | All patients were replaced with a new allograft | One patient chose amputation due to limb salvage failure |
| Errani *et al.*[33] | 2020 | 11 | 45% | Three cases were treated with immobilization, and nine cases underwent reoperation (bone grafting or internal fixation) | Two cases failed to reoperate |
| Frisoni *et al.*[17] | 2012 | 71 | 27% | One was treated with immobilization and four with a vascularized fibular graft; 15 cases were treated with bone grafting and fixation | The failure rate of reconstruction was 77% |
| Han *et al.*[24] | 2014 | 17 | 12% | One treated with bone grafting only and one with bone grafting and internal fixation | One case of refracture |
| Houdek *et al.*[34] | 2018 | 11 | 45% | All allografts were revised | Fractures healed |
| Lun *et al.*[28] | 2018 | 18 | 17% | Revised to a combination of an autologous fibular graft with a new allograft | Fractures healed |
| Muscolo *et al.*[35] | 2004 | 59 | 7% | Two had another intercalary graft, and one had conversion to an osteoarticular allograft. The remaining patients required endoprostheses | Not described |
| Aponte-Tinao , *et al.*[36] | 2019 | 198 | 15% | Three patients were treated with internal fixation and addition of autologous graft and 14 patients were treated with a second intercalary allograft. 12 patients were treated with endoprostheses | Six patients failed and were treated with a second allograft |
| Aponte-Tinao , *et al.*[25] | 2015 | 135 | 14% | Six patients were treated with internal fixation and addition of autologous graft and 13 patients were treated with a second intercalary allograft | Three patients failed and were treated with reoperation |
| Garcia-Coiradas, *et al.*[18] | 2015 | 39 | 12.8% | All patients were treated with new internal fixation and allografts were preserved | Not described |
| Gharedaghi[19] | 2016 | 102 | 5.9% | All patients received replacement with larger plates to correct fractures, and autologous bone transplantation was used to promote healing | Not described |
| Thompson *et al.*[26] | 2000 | 74 | 42% | 16 cases were treated with autologous bone grafts, and five cases underwent knee surface replacement. 10 patients underwent prosthetic replacement or amputation | Fractures of patients with autologous bone transplantation healed |

biological intramedullary nail allows early weight-bearing and patient function, which is conducive to bone growth. Compared with non-biological intramedullary nail fixation, it has more contact area that is better for bone integration. The follow-up results 44 months after the operation showed that long-term effective fixation was achieved by good matching and osseointegration between the intramedullary nail system and the bone interface, although the healing of the allograft bone fracture did not occur well. Therefore, the outcome of this case is satisfactory. The effectiveness of a 3D customized technique combined with a fully coated biological intramedullary nail in the treatment of different sites and different types of allograft bone fractures is one of the directions of future research.

There is an obvious deficiency in this case. According to the research results of Falzarano, it is suggested that different fixation methods for the distal tibia have an impact on gait, and the weight of heel and metatarsal also changes according to different fixation methods.[32] It is a pity that this study did not evaluate the impact of the patient's fixation on gait and foot weight-bearing relative to other fixation methods.

## Conclusion

Allograft bone transplantation and reconstruction is a method worth considering in the treatment of diaphyseal bone loss. Satisfactory results can be achieved through appropriate planning, although there are possible serious complications. The use of a 3D customized technique to develop an individualized internal fixation is a good choice to manage the complications associated with bone allograft fractures. In this case, the good osseointegration of the interface between the biological intramedullary nail system that we developed and the host bone can lead to a long-term effective fixation.

## Ethics Approval and Consent to Participate

This study has been approved by the Biomedical Ethics Committee of West China Hospital of Sichuan University [Approval No.: 2019 (0419)], and written informed consent was obtained from the patient.

## Authors' Contributions

HY collected and analyzed the data, prepared the manuscript. WZ participated in the surgical operation, collected, and analyzed the data, and prepared the manuscript. XF prepared the manuscript. YX collected and analyzed the data, prepared the manuscript. HD principal surgeon, collected and analyzed the data, supervised the writing of the manuscript. All authors have read and approved the manuscript.

## Conflicts of Interest

The authors declare that they have no conflicts of interest pertaining to this study.

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