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Extracorporeal Irradiation and Reimplantation of Tumor-bearing Bone Segments Following Diaphyseal Sarcoma Resection at the Tibia

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Abstract. *Background/Aim: Reconstruction of diaphyseal tibial sarcomas with extracorporeal irradiated autograft is a rarely applied technique and is analyzed in this study. Patients and Methods: Eight patients with malignant sarcomas received local treatment by means of a wide resection and reimplantation of an extracorporeally-irradiated autograft. The graft was combined with an ipsilateral vascularized fibula when a full-thickness segment of the tibia had to be resected and no cortex could be preserved (n=5). Oncological and functional results were recorded. Results: All patients had clear margins after resection, and with no local recurrence 72 months after treatment. Full weight-bearing was allowed at the time of radiological consolidation of the irradiated grafts (after a median of five months). The functional results were good and excellent in 7 of 8 patients, respectively. Conclusion: Extracorporeal irradiation grafting is a suitable method for the treatment of localised and resectable tibial sarcomas.*

Diaphyseal sarcomas at the tibia are rather rare and sometimes challenging due to the reduced soft tissue coverage, as well as the poor blood supply (1). Common treatment options include wide resection and reconstruction with intercalary endoprostheses, as well as biological strategies such as distraction osteogenesis, the induced membrane technique, or vascularised/non-vascularised bonegrafts (2).

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Tumor prostheses allow early full weight-bearing and usually provide good functional results (3). However, intercalary endoprostheses at the tibia are prone to complications such as infection and aseptic loosening, which occur in over 35% of patients (3, 4). Therefore, biological reconstructions are recommended in children and adolescents. The endogenous induction of osteogenesis, *e.g.* by means of callus distraction or the induced membrane technique, is, in principle, one of the best reconstruction methods in pediatric tumor patients. Nevertheless, treatment time using external fixation is rather long and applicability of intramedullary segmental transport systems is reduced, especially in bone defects that are closely related to the joint.

A further promising autologous treatment option, therefore, is the reimplantation and osteosynthesis of the tumor-bearing bone segment following annihilation of all tumor cells. The latter can be achieved by treatment with liquid nitrogen, pasteurisation, microwave radiation, autoclavation, or extracorporeal irradiation (5). In contrast to allografts, this method comprises additional advantages such as perfect graft dimensions and fit at the osteotomy site, easy osteosynthesis conditions, as well as avoidance of immunological response (5). At our Department, two common techniques are used: reimplantation of the extracorporeally irradiated bone segment and reimplantation of the irradiated bone segment in combination with the ipsilateral vascularized fibula (tongue in groove technique)

The purpose of this study was to analyze our results of these two procedures with regard to the oncological and functional outcome, as well as complications after tumor resection. Additionally, we evaluated the indication for either technique and compared the outcome with other treatment options in the literature.

Patients and Methods

Patients. In total, eight patients with diaphyseal sarcomas at the tibia or soft tissue sarcomas of the lower leg attached to the tibial

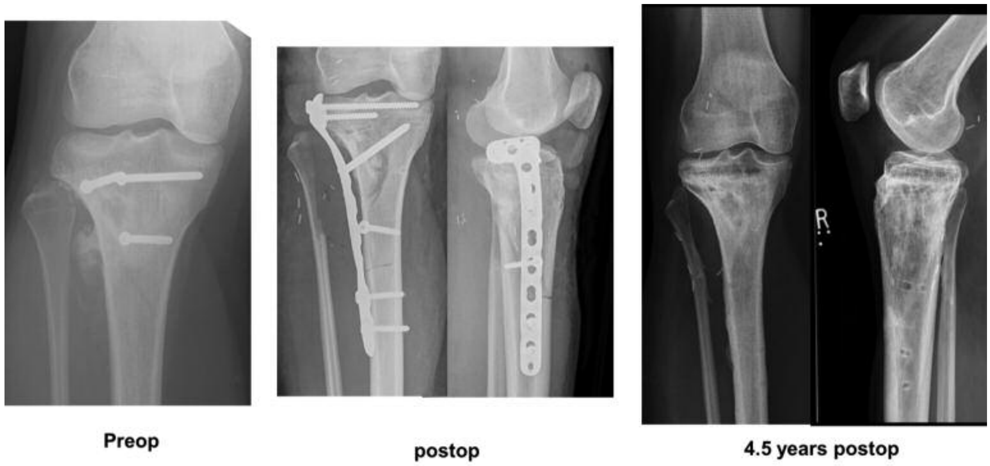

Figure 1. *Follow-up of a 23-year-old female with a dedifferentiated osteosarcoma as recurrence of an initial low-grade paraosteal osteosarcoma (a). During resection, the medial cortex was preserved and the resected segment reimplanted after extracorporeal irradiation (b). Complete bony integration and consolidation is visible at the latest follow-up after metal removal 72 months postoperatively (c).*

Table I. *Patient data.*

Case No.	Gender	Diagnosis	Relevant preoperative side diagnosis	Age at diagnosis (Years)	Metastases	Neoadjuvant chemotherapy	Response chemotherapy non or good responder	Resection tibia length (cm) fibular graft	Reconstruction with vascularised
1	F	Chondrosarcoma G1	Paraplegic, mobilized in wheelchair	48	No	No		7	No
2	F	Dedifferentiated osteosarcoma G3	St post resection of a paraosteal osteosarcoma (low grade) same site	23	No	Postop chemo		9	No
3	M	Myofibroblastic Sarcoma G2	No	59	No	No		6	No
4	F	Adamantinoma	Posttraumatic arthrosis at the ankle of the other side - already on crutches	23	No	No		22.5	Yes
5	M	Ewing's Sarcoma	No	12	No	Yes	Good	12	Yes
6	F	Adamantinoma	No	11	No	No		15	Yes
7	M	Ewing's Sarcoma	No	39	No	Yes	Good	11	Yes
8	M	Rhabdomyosarcoma	No	12	No	Yes + radiation	Non	18	Yes

shaft, who were treated with wide resection, extracorporeal irradiation (ECI), and reimplantation, were included in this study. The median age at the time of diagnosis was 23 years (range=11-59 years); 3 patients were still skeletally immature. No patient showed metastatic disease at the time of diagnosis. Patient characteristics as well as the underlying tumor entities are listed in Table I. Three out of eight patients received neo-adjuvant chemotherapy, and one patient received adjuvant chemotherapy postoperatively.

Data presented in this study obtained approval by the local ethics committee (Ethikkommission Nordwest- und Zentralschweiz - number of approval: Nr.2012-83).

Operative technique. The surgical plan included wide *en-bloc* resection with clear margins, complete excision of biopsy scars, ECI, and reimplantation of the resected tibial segment.

In three patients, one tibial cortex as well as the overlying periosteum could be preserved without compromising the

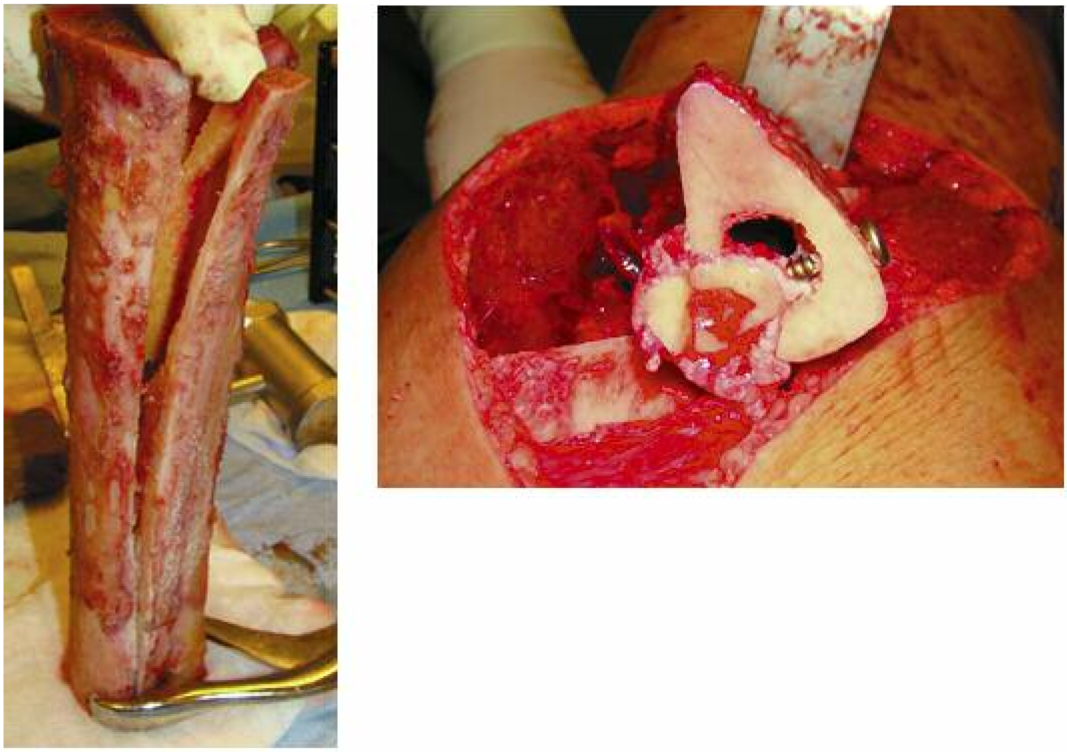

Figure 2. *Tongue in groove Technique (left) and reimplantation of the extracorporeally irradiated autograft as composite with the vascularized fibula (right image).*

oncological resection margins (proved by intraoperative frozen section analysis) (Figure 1). In these cases, the irradiated bone was re-implanted without an additional ipsilateral fibula.

In five patients in which the affected segment had to be resected in full thickness without leaving one cortex *in situ*, the extracorporeally irradiated autograft was re-implanted together with the ipsilateral vascularized fibula (Figures 2-4). Therefore, a groove was cut into the autograft in order to fix the vascularized fibula (Figure 2).

In any case, obvious tumor tissue was carefully removed for histological evaluation after resection of the tibial segment. Important soft tissue structures like tendons (particularly the patellar tendon) were preserved to ensure reinsertion after reimplantation and hence good functional outcome (Figure 5a). After preparation, the resected bone segment was wrapped in saline soaked gaze and vacuum-sealed in three sterile plastic bags. The latter procedure was made in order to prevent air bubbles, which may reduce the effect of irradiation. Afterwards, the package was brought to the radiotherapy Department and the bone was irradiated isocentrically (opposed fields) with a homogeneous dose of 50 Grays (Gy) using 6 MV photons at a dose rate of 1.8 to 2.0 Gy per min, which took about 25-30 min (Figure 5b).

During the radiation process, biopsies were taken from the proximal and distal osteotomy sites as well as from the preserved cortex (if available).

The ipsilateral fibula was carefully prepared with the nutrient branch of the peroneal artery and veins by the senior author. The fibula was then osteotomized with a total length of 2 cm longer than the resected tibia (5-10 mm at each side). The returned irradiated tibia was intensively scrubbed with betadine solution for disinfection, and a fibular bed was prepared by means of a trench, which was cut dorsolaterally into the cortex of the irradiated bone segment (tongue in groove technique) (Figure 2). The fibula was then carefully adjusted into the groove, avoiding tension to the peroneal nerves and the pedicle. The fibula was fixed in the tibial groove using a 2.7 screw (Figure 2) with an overlap of 5-10 mm at each side. Finally, the construct was re-implanted into the segmental defect and stabilized with a single locking plate. In cases where the osteotomy was quite metaphyseal, an additional small second plate was used at the osteotomy site.

Patients were ordered bed rest with elevated lower limbs for one week postoperatively. Afterwards, mobilization was started on crutches with touch-down weight-bearing for a minimum of 3 months. After this phase, patients started partial weight-bearing depending on callus formation of the vascularized fibula on x-rays. Full weight-bearing was allowed when either bridging of the osteotomies between irradiated bone and host bone was found, or the vascularized fibula revealed hypertrophy according to the De Boer's study (6).

Regular clinical and radiological follow-up examinations were performed in our oncological orthopedic outpatient clinic every 6 weeks until complete consolidation. Delayed union was defined as incomplete bony consolidation after 12 months of time, whereas non-union was assumed after 24 months. CT-scans of the lungs were acquired according to the postoperative examination protocol to exclude metastatic disease. The functional outcome was assessed using the Musculoskeletal Tumour Society (MSTS)- Score (7) and the regained percentage of preoperative activity level.

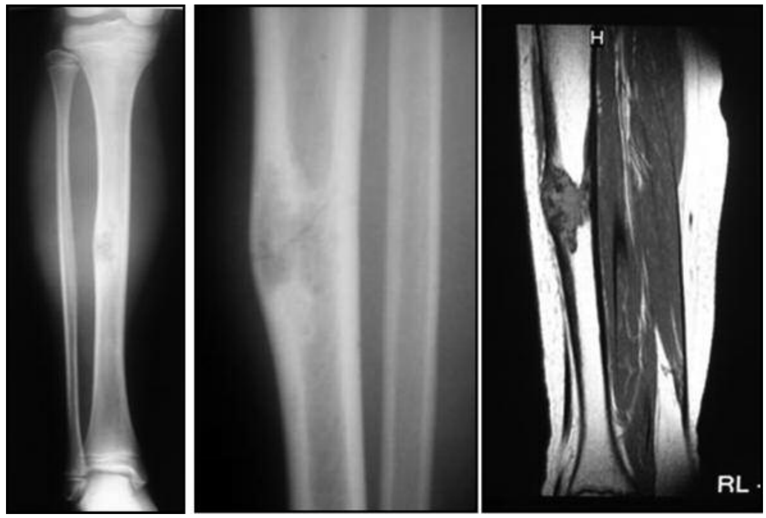

Figure 3. *Eleven-year-old female patient with an adamantinoma of the right diaphyseal tibia. Typical radiographical appearance of the adamantinoma on conventional radiographs (left and middle) and magnetic resonance imaging (MRI) scan (right image).*

Figure 4. *Postoperative follow-up after 3 months (first), 12 months (second) and 60 months after removal of metal (third and fourth image).*

Due to the low number of patients, description of data was based on medians and the minimal and maximal range for continuous endpoints. Event-free and overall survival was calculated from the time of histological diagnosis to the latest uneventful follow-up visit. An event was defined as a relapse or progression of disease, a treatment-related secondary neoplasm, or death. An event affecting the overall survival was defined as death from any cause.

Results

Clinical findings. The median follow-up was 72 months (range=60-112 months) for all patients, and all of them survived. All patients were free of distant metastases at the time of diagnosis as well as at the latest follow-up. All high-grade

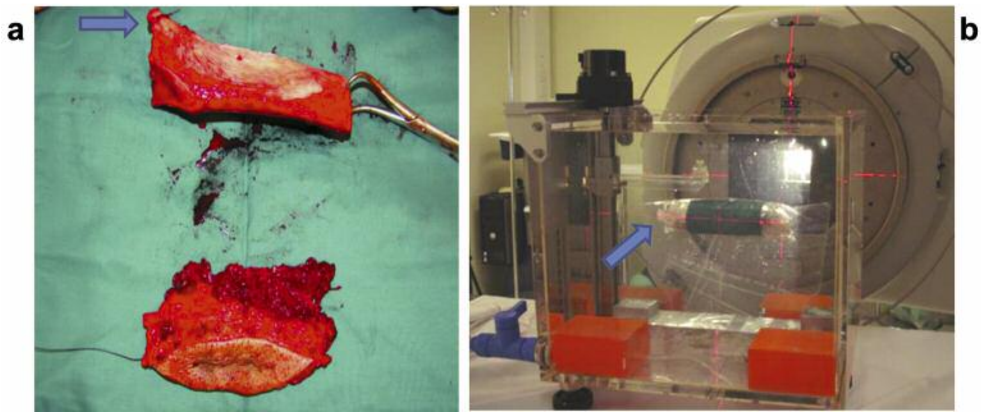

Figure 5. *After resection of the tumor-bearing segment obvious tumor tissue as well as the biopsy tract are removed, whereas important functional structures such as the patellar tendon (⇨) are spared (a). Setup at the linac: wrapped resected bone (⇨) positioned in a small water phantom set on the linac couch (b). Duration of radiation therapy: 25-30 min.*

sarcomas (n=4, cases 2, 5, 7, 8) received postoperative chemotherapy, three patients (cases 5, 7, 8) neo-adjuvant therapy, respectively. Histological findings revealed good response to chemotherapy in two patients (cases 5, 7) with less than 10% viable tumor cells. All biopsies taken from the osteotomy sites showed clear margins, and none of our patients has been diagnosed with recurrent disease. In one case (case 8, Rhabdomyosarcoma), additional radiotherapy was applied postoperatively because of close margins (5 mm) and non-response to neoadjuvant chemotherapy.

The median length of the resected tibial segment was 11.5 cm (range=6-22.5 cm), the vascularized fibula (cases 4-8) was median 1.7 cm longer (range=13-24 cm) than the tibial segment. The median operating time was 6 h (range= 5-8.5 h), of which approximately 45 min were taken up for transporting the bone to and from the radio-oncological department to be irradiated.

Functional results. Full weight bearing was allowed after a median of 5 months (range=3-7.75 months). One patient with a preexisting paraplegia had to use a wheelchair. The median MSTS score was 76.4% (IQR=61.5 to 92; range=51-100) and 84% (range=63-100) for patients who achieved complete bony union.

Radiological findings. Complete bony union was achieved in 14 of 16 osteotomy sites after a median of 4.3 months (range=3-6 months) at the proximal osteotomy site, and 6.9 months at the distal site (range=5-11 months). Two osteotomy sites in two patients with combined fibula reconstruction (cases 4, 5) showed delayed union after a mean of 24 months, but finally healed after 27 (case 4) and 30 months (case 5). Once union of the vascularized fibula occurred, hypertrophy of the junctions was seen in 4 patients. In all but one patient (case 5) who showed an atrophy of the vascularized fibula after perioperative complications (vasospasm), there was a mean fibular hypertrophy of the proximal sites of 40.5% (range=14-73.5%) and 17.8% for the distal fibular sites (range=11.5-25 %) within 37.8 months on average (range=22-76 months). The fibula was integrated into the tibia after a median of 33.5 months (range=27-40 months).

Complications. Local complications occurred in four patients, all of which required revision surgery (Table II).

One patient with a combined tibia and fibula reconstruction (case 5) showed a vasospasm of the popliteal artery 12 h after the initial procedure, and sustained a compartment syndrome 48 h after revision surgery with a painful neuropraxia of the N. peroneus profundus. In the second look exploration, a (partial) necrosis of the tibialis anterior muscle was obvious, which required resection. Therefore, a drop foot is still persisting in this patient.

Two patients (cases 5 and 8) presented with wound breakdown and superficial infection at the lower leg due to direct trauma, requiring plastic reconstruction. One patient (case 5) had an incised wound directly at the level of the underlying plate. The other (case 8) fell from his bike and suffered a fracture at the proximal osteotomy site. Patient 5 additionally developed a deep infection with contamination of the locking plate. Therefore, the plate was removed, an intramedullary nail was inserted, and the wound closed by a local flap reconstruction. In patient 8 who had received neoadjuvant percutaneous irradiation, the distal part of the surgical wound showed delayed healing and was in need of further plastic revision. In both patients, complete healing was achieved after the above-mentioned interventions.

One patient (case 4) presented with a delayed union at the proximal osteotomy site and a deep infection due to a screw perforation in this region. After screw removal, the patient

Table II. *Outcome data.*

					Time to union	Time to union	Hypertrophy Index of the fibula		De Boer Index				
Case No.	Follow-up (months)	Biopsies of the margins	Disease status	Time to full weight bearing (months)	Proximal OT side (months)	Distal OT side (months)	Proximal OT preop till last follow-up (mm)	Distal OT preop till follow-up (mm)	Resection fibula last length (cm)	Fibula index (%) proximal	Fibula index (%) distal	Complications and second procedures	MSTS + (%)
1	72	Clear	NED[a]	Wheelchair	6	10	No	No					84
2	72	Clear	NED	4	4	8	No	No					63
3	96	Clear	NED	3	3	6	No	No					100
4	60	Clear	NED	5.25	27 - delayed	11	14.25/ 18.78	12.12/ 15.14	24	32	25	Infection of the subcutaneous anterior screws[b]	51
5	66	Clear	NED	7.75	3	30 - delayed	9.72/ 7.47	14.00/ 10.40	13	-23	–34.5	Vasospasm postop[c], Direct trauma with 2° deep infection[d]	60
6	108	Clear	NED	6	6	6	13.92/ 15.88	12.17/ 14.41	16	14	18.5		81
7	84	Clear	NED	5	4	6	13.91/ 24.11	17.02/ 18.95	13	73.5	11.5		100
8	60	Clear	NED	4	4	5	20.26/ 28.84	17.68/ 20.55	21	42.5	16.25	Direct trauma with wound break down[e]	72

[a]NED: No evidence of disease; [b]Case 4: Removal of the screws, local debridement, Antibiotics *i.v.*/oral; [c]Case 5: Revascularisation and vessel bridging with autograft, fascietomy and removal of necrotic muscles; [d]Case 5: Vascular muscle flap and implant change from plate to nail; [e]Case 8: Vascular muscle flap.

had intravenous antibiotics for two weeks and oral antibiotics for three months, respectively. Once the infection was healed, consolidation of the proximal osteotomy site occurred without any further interventions.

The incidence of deep infection was 25% (2 of 8) in our collective, whereas all had a composite reconstruction consisting of the irradiated bone segment and a vascularized fibula. Additionally, all of our complications were recorded in patients who received chemotherapy postoperatively. There was no association between the occurrence of complications and the length of the resected bone segment or patient's age. Stress fractures were seen neither in the tibia nor in the fibular autograft.

Discussion

We retrospectively enrolled eight patients with diaphyseal sarcomas at the tibia or soft tissue sarcomas of the lower leg attached to the tibial shaft, who were treated with wide resection of the affected tibial segment, extracorporeal irradiation (ECI), and reimplantation. In five cases, the extracorporeally irradiated graft was combined with an ipsilateral vascularised fibula. All patients had clear margins after wide resection and were free of disease at the latest follow-up. In total, three postoperative complications were recorded. Bony consolidation was achieved after a median of five months, the vascularized fibula autografts showed a significant hypertrophy in 8 of 10 junctions. Functional results were good and excellent in 7 and 8 patients, respectively.

Diaphyseal sarcomas at the tibia are rare. Analyzing the database of our national bone tumor reference center revealed that only 5% of children and 2.3 % of adults had solid bone tumors at this localization (1). The prognosis of patients with primary diaphyseal tumors at the tibia is relatively good. This is probably due to the fact that the antero-medial aspect of the tibia is lying subcutaneously. Pain as well as tumor-related swelling occur at an early stage in most cases and can be detected easily. In our series, all patients survived with a good functional outcome. Likewise, in the literature, survival rates up to 93% are reported with good to excellent results at this location (8, 9).

Good survival rates, however, require a sufficient local tumor treatment beside a proper and patient-specific reconstruction concept. The tibia itself presents special anatomical conditions, which may increase the risk of complications. Therefore, specialized tumor centers should be able to offer different and individualized treatment solutions in order to achieve the best possible result for any patient. Popular operative techniques include reconstructions with contralateral vascularized fibular grafts and/or an allograft, segmental transports, intercalary endoprosthetic replacements, and the induced membrane technique (9-16).

Each reconstruction technique has its advantages and disadvantages. The use of the contralateral fibula grafts – either vascularized or non-vascularized - might be a useful method, particularly in younger patients, as remodeling of the resected tibial segment by hypertrophy is possible (12, 17). Disadvantages are – among others - the high risk for stress fractures, donor site morbidities, as well as involving the "healthy" leg (12). For reducing the donor site morbidity, the use of allografts could be an attractive option, but is also known to be complication-prone. Furthermore, a quick availability of allografts depends on the presence of a bone bank in order to match proper dimensions as needed for the resected bone segment (18, 19). Although excellent results have been achieved in some studies (10), the risk of fractures (7-42%), infections (5-30%), and non-unions (9% to 63%) can be high (16, 20-22). Therefore, Capanna *et al.* described a reconstruction method for intercalary bone defects combining the use of a tibial allograft and a free vascularized fibular graft (10). Like in our technique with the use of an irradiated autograft, the prepared allograft provides initial biomechanical stability, while the vascularized fibula is supposed to improve bony union and hypertrophy within the allograft over time. The main disadvantage of this technique is the long operating time (mean 8.5 h), the need of a microvascular surgeon to perform the vascularized fibular graft, and the donor site morbidity. Additionally, full weight-bearing is not allowed for a long time (mean 21.4 months after surgery) with a mean time to union of 19.6 months (10). Nevertheless, Capanna's patients achieved excellent functional results and a limb salvage of 79% after five years (10).

The concept of callus distraction or the induced membrane are well-established biological reconstruction methods for bone defects following chronic osteomyelitis, traumatic bone loss, or septic/aseptic non-unions (13). However, although both techniques have their advocates, they are relatively time-consuming, painful, and complication prone, particularly if large defects have to be bridged and chemotherapy is to be received (11, 23). For the induced membrane technique, infection rates of up to 43% have been reported, which might be attributed to the 2-stage character of this method (24).

Cemented intercalary endoprosthetic replacements are a good option, too, especially in older patients with reduced bone quality. Endoprosthesis allows immediate full weight-bearing and provide a good as well as predictable functional outcome (3). Long-term results, however, are more controversial: failure due to complications such as infections or aseptic loosening occurs in over 35% of cases (3, 4). Therefore, endoprosthesis may be a good indication for patients with a limited life expectancy, whereas they are not a first-choice procedure in younger patients with a good prognosis.

The technique of wide resection, extracorporeal irradiation, and reimplantation (ECI) has the advantage of being a biological reconstruction method with the potential for long-term survival (25, 26). Furthermore, reimplantation spares the acquisition of a suitable allograft, and is therefore an appropriate treatment option for *e.g.* Asian countries, too, in which the use of allografts is not allowed due to ethical reservations. Beside the perfect anatomical fit of the irradiated graft, structures as ligaments or tendons can be preserved with this technique. This led to appealing functional results in our series (median MSTS score of 76.4%), comparable to those previously described in the literature for different reconstruction techniques at the tibia (74-92%) (3, 10, 27, 28). Considering the fact that two of our patients had a preexisting functional impairment (wheelchair and walking aids), which is not taken into account in the MSTS score, our results appear to be even better. Likewise, higher functional results have been reported using the ECI technique, at least at different anatomical locations (29-31).

At the tibia, the medial surface is lying quite subcutaneously, whereas stabilizing plates have to be positioned directly under the skin. We, therefore, routinely cover long composite reconstructions (irradiated autograft and vascularized fibula) with a medial gastrocnemius flap (n=5), which is an essential principle in the implantation of tibial tumor prostheses, too, in order to decrease the infection rate (32). With this method, a muscular coverage of the proximal two thirds of the reconstruction can be achieved. Nevertheless, the distal part is still at risk of wound complications and secondary implant contamination, as seen in one of our patients (case 5).

A further anatomical fact is the poor vascular blood supply at the distal tibia, which is well described in the literature (33). Therefore, according to our experience, the distal osteotomy of diaphyseal reconstructions, which often extends down to the distal third of the tibia, needs longer time to consolidation. This assumption is supported by our results, showing a (radiologically) significantly faster consolidation time at the proximal tibia (4.3 months) compared to the distal osteotomy (6.9 months). Thus, proximal osteotomies united almost in half the time compared to distal osteotomies. Two cases of delayed union (14 of 16 osteotomy sites – one proximal and one distal osteotomy) were caused by local infections. After local infection control, bone consolidation was observed without any additional problem. Shorter defect reconstructions in which one cortex could be preserved (n=3) did not show any delayed union or local complications, such as wound problems or infections. Thus, the complication rate in our series was comparable to different reports using the ECI technique (8).

One shortcoming is that this technique can be applied only in cases where the biomechanical properties of the bone are not too much affected by the tumor (25, 30). Furthermore, a proper histopathological examination with regard to resection margins and response rate after neoadjuvant chemotherapy (high-grade bone sarcomas) is not possible with this technique. However, we believe that biopsies from the osteotomy interface as well as the tumor tissue removed before irradiation should be sufficient to assess both. This is supported by the low recurrence and mortality rate in our series and the results previously reported in the literature (25, 30, 31).

The study is mainly limited by the small sample size as well as the heterogeneous study population (different tumor entities, reconstruction with/without vascularized fibula). Furthermore, no control groups with different reconstruction techniques were included.

In conclusion, extracorporeally irradiated autografts with/without vascularized fibulae are a suitable reconstruction method for diaphyseal bone defects at the tibia following resection of malignant tumors. Best results were obtained in cases where one cortex and the periosteum could be preserved. Complication rate and functional results (good to excellent) were comparable to alternative treatment options in this anatomical region.

Conflicts of Interest

The Authors declare that there are no conflicts of interest and no financial support regarding the present study.

Authors' Contributions

AHK and MH performed all operations and designed the work; MWG performed the extracorporeal radiation; LS collected the data and wrote a draft; AHK wrote the manuscript; MWG, MH, UL and AHK performed the data analysis and interpretation; UL and MWG critically reviewed the manuscript.MH and AHK edited and finalized the manuscript.

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