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Original Article

Preoperative radiotherapy negatively affects early hypertrophy but has no effect on graft survival and union in patients treated with vascularized fibular grafts for bone tumors

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ABSTRACT

Background: Preoperative radiotherapy may impair bone healing and remodeling after wide resection and reconstruction using vascularized fibular grafts for bone tumors. This study evaluated whether preoperative radiotherapy affected union, nonunion, graft viability, and graft hypertrophy in these patients.

Methods: We retrospectively reviewed data from 127 patients who underwent wide resection of a bone tumor and reconstruction with a vascularized fibular graft (2000–2023). Outcomes included time to initial and complete union, nonunion at 12 months, graft viability, graft hypertrophy at 3, 6, and 12 months, and the Musculoskeletal Tumor Society score. Patients were compared based on whether they received preoperative radiotherapy.

Results: The mean age was 16.6 ± 11.3 years, and osteosarcoma and Ewing sarcoma were the most common diagnoses. The femur (48.8%) and tibia (34.6%) were the most affected sites. Thirty-one patients received preoperative radiotherapy, and nine received postoperative radiotherapy. The initial union time was 5.6 ± 2.1 months, and the complete union time was 11.3 ± 3.2 months. Nonunion at 12 months occurred in 20 patients (15.7%), and graft viability was preserved in 122 patients (96.1%). The mean hypertrophy increased from 16.1 ± 11.6% at 3 months to 29.8 ± 17.8% at 6 months and 46.2 ± 28.0% at 12 months. Patients who received preoperative radiotherapy demonstrated lower hypertrophy at 3 and 6 months ($P = 0.013$ and $P = 0.005$), with no statistically significant difference at 12 months. The mean Musculoskeletal Tumor Society score at final follow-up was 24.2 ± 5.4 (range, 2–30).

Conclusion: Preoperative radiotherapy was associated with reduced graft hypertrophy at 3 and 6 months, with no statistically significant difference at 12 months, and did not adversely affect graft union or viability, supporting vascularized fibular graft reconstruction when radiotherapy is required for oncologic local control.

Level of evidence: Level III, prognostic study.

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1. Introduction

Appropriate chemotherapy (CT) and radiotherapy (RT) protocols improve the survival of patients with malignant bone tumors [1]. Malignant bone tumors are usually diagnosed in the second decade of life with the goal of having the longest possible

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functional and survival time. There are two main treatment options for primary malignant bone tumors: biological reconstruction and endoprosthesis [2]. There are several options for reconstructing large bone defects after wide resection of malignant tumors, including massive allografts, osteoinductive membrane techniques, bone transport, cortical struts, and vascularized fibular grafts (VFG) [3,4]. Currently, depending on the length of the vascular pedicle and ease of access for harvesting, VFG is often used to restore large segmental bone defects [5]. VFG offers many advantages, such as early osteotomy union and spontaneous healing after fracture; it retains the ability to hypertrophy under mechanical stress, even in critical soft tissue conditions [6].

In the case of malignant bone tumors, wide resection may not be possible because of the proximity and invasiveness of the tumor to the surrounding vascular or neural tissue. In these cases, preoperative RT may help achieve more reliable local control [7]. RT is not used as a first-line treatment for resectable osteosarcomas, chordomas and chondrosarcomas, but surgical resection and radiotherapy have become standard options for local control for Ewing's sarcoma [8]. However, the success of treatment outcomes can also be affected in patients who undergo biological reconstruction following either preoperative or postoperative RT.

Our hypothesis in this study was that preoperative radiation therapy would decrease the union rate of the VFG. The aim of this study was to compare graft union and hypertrophy in patients with bone tumors who underwent wide resection and reconstructed with VFG, who received preoperative RT, and who did not receive preoperative RT.

2. Materials and methods

We used a database of four orthopaedic oncologists to evaluate data from patients diagnosed with bone tumors and treated with wide resection and biological reconstruction with VFG between 2000 and 2023. The study was approved by the Institutional Review Board of the Department of Orthopaedics and Traumatology as well as the Institutional Ethics Committee prior to commencement, and all patients and their parents provided written informed consent. Medical and surgical histories, radiographs, and other radiological images were evaluated and reviewed from the medical registration files of the oncologic orthopedic department.

This study included patients diagnosed with bone tumors who underwent wide resection followed by VFG reconstruction, were primary cases, had a follow-up duration of at least 12 months postsurgery, and had comprehensive demographic, medical, radiological, and surgical records available. Patients were excluded if they had metastatic bone tumors treated with wide resection and non-biological reconstruction, received fibular grafts without vascularization, were revision cases or had unplanned resections, underwent VFG for nonunion, had a history of osteomyelitis, or declined participation in the study (Fig. 1).

Indications for VFG reconstruction: A vascularized fibular graft was selected for reconstruction after wide resection when a durable biological reconstruction was preferred, particularly for intercalary defects of the femur or tibia and/or large segmental defects where long-term remodeling and hypertrophy under load were desired. Additional indications included young age, expected long-term survival, limited soft-tissue envelope, prior infection risk, or when endoprosthetic reconstruction was considered suboptimal. Benign aggressive lesions (e.g., giant cell tumor of bone or fibrous dysplasia) were included only when wide resection was indicated because of aggressive behavior, location, or recurrence risk.

Patient management and operation procedures: A detailed history and physical examination were performed on patients admitted to our outpatient clinic with mass or pain in the musculoskeletal area. All patients underwent radiography followed by contrast-enhanced magnetic resonance imaging of the entire limb. For histopathological diagnosis, a core needle biopsy was performed by the operating surgeon. After evaluation of histological specimens, treatment was approved by a board consisting of an orthopaedic oncologist, adult and pediatric oncologists, a radiation oncologist, a pathologist specialized in the musculoskeletal system, and a musculoskeletal radiologist. Based on the board's decisions, patients received neoadjuvant CT, neoadjuvant RT, or direct surgical resection.

RT protocols: RT was prescribed by the radiation oncology department according to diagnosis-specific protocols and oncologic indications, in line with contemporary standards of practice. Preoperative RT was not used routinely as a standard regimen for osteosarcoma. In osteosarcoma, it was reserved for selected patients with an extensive soft-tissue component when the multidisciplinary tumor board considered additional local control necessary. For Ewing sarcoma and Ewing-like tumors, RT was delivered using conventional fractionation (typically 1.8–2.0 Gy per fraction) to total doses consistent with established local control regimens (approximately 45–55.8 Gy; about 25–31 fractions, including boosts when indicated). In selected cases requiring preoperative RT (e.g., extensive extraosseous disease or proximity to critical neurovascular structures), surgery was planned after recovery from acute radiation effects, typically 3–6 weeks after RT completion. In all patients who received RT, the recipient vessels used for microvascular anastomosis were located within the irradiated field. A summary of diagnosis-specific RT protocols is provided in Supplementary Table S1.

CT protocols: Systemic therapy was administered according to histological diagnosis using diagnosis-specific institutional protocols consistent with contemporary standards and multidisciplinary tumor board decisions. Protocols were updated over time as evidence and guidelines evolved. Osteosarcoma patients received multi-agent CT based on high-dose methotrexate, doxorubicin, and cisplatin (MAP-based regimens). Ewing sarcoma/Ewing-like tumor patients were treated with vincristine, doxorubicin, and cyclophosphamide alternating with ifosfamide and etoposide (VDC/IE), including interval-compressed schedules when applicable. Other malignant mesenchymal tumors of bone were treated according to subtype-specific contemporary sarcoma protocols determined by medical oncology, typically doxorubicin-based multi-agent regimens when chemotherapy was indicated. CT was not routinely administered for chondrosarcoma, adamantinoma, or benign aggressive lesions. A summary of diagnosis-specific systemic therapy and radiotherapy protocols is provided in Supplementary Table S1, and treatment exposure by diagnosis is provided in Supplementary Table S2.

Four orthopaedic oncology specialists performed all surgical procedures with wide resection and excision of the biopsy tract. The bone osteotomy level was determined by preoperative magnetic resonance imaging measurements and confirmed by fluoroscopy during operation. The surgical margin was assessed using frozen-section histopathology. After tumor resection, recipient vessels for biological reconstruction with VFG were dissected and marked. The resected bone was scraped from soft tissue for cryoablation on a separate table. Four experienced microsurgeons performed microsurgery treatments. The fibular bone was removed except for 4–6 cm to preserve the peroneal nerve and 6 cm for ankle stability [9]. The VFG was fixed with plates or nails, particularly in lower extremities. The microsurgeon performed pedicle anastomosis after fixation. Cryoablated host tissue was

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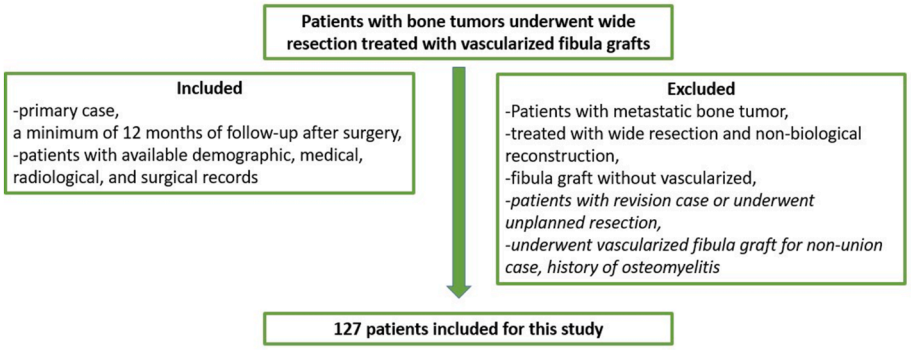


Fig. 1. Flowchart of patients.

used for reconstruction without allografts. VFGs were placed inside resected and cryoablated bones with openings for vascular structures, without skin paddles. Separate drains were used for the harvest and resection areas. The algology department was consulted for postoperative pain control.

All histopathological examinations after biopsy and definitive surgery were performed by musculoskeletal pathologists. In all cases, surgical margins were negative (R0).

Postoperative management and rehabilitation: Rehabilitation began on postoperative day 1 as tolerated. Time to full weight bearing was defined as the time from surgery to patient-reported and clinician-confirmed full weight bearing without external support; progression to full weight bearing was individualized according to fixation stability, symptoms, and radiographic healing. Ambulation was initiated using crutches or a walker with toe-touch weight bearing (TTWB) when appropriate to fixation stability. TTWB was defined as approximately 20% of total body weight per current literature. [10] Patients were initially trained using a scale to understand TTWB, which was discontinued as they became consistent. Weight bearing was then progressively advanced based on fixation strength and radiographic healing. Joint range of motion began with orthosis support. Patients were discharged after achieving pain control and mobilization. Postoperative anteroposterior and lateral radiographs were obtained after drain removal and before discharge. Patients were followed up at 1 and 3 weeks for wound and radiographic control, then referred for adjuvant therapy. Graft union was monitored through monthly radiographs for the first 3 months, and at the 3rd, 6th, and 12th months. They underwent contrast-enhanced MRI at the 3rd, 6th, and 12th months for recurrence control, and chest computed tomography or positron emission tomography for metastasis screening. Local computed tomography scans were used only for delayed union or nonunion cases.

Radiological evaluation: Radiographic measurements were performed by a single author using digital PACS software (Extreme PACS) according to a predefined measurement protocol. Successful bone union was defined as bridging callus across $\geq$3 of 4 cortices on each side of the graft-host junction on both anteroposterior and lateral radiographs.

The initial bony union time was defined as the interval between the surgical procedure and the first radiographic evidence of consolidation in at least one of the four cortices. Complete bony union time was defined as the interval between the surgical procedure and the first radiographic evidence of consolidation of at least three of the four cortices on both the proximal and distal sides of the VFG-host bone junctions on anteroposterior and lateral plain radiographs. Union times were calculated among patients who achieved union; patients meeting the study definition of nonunion at 12 months were not assigned a union time and were analyzed separately as a categorical endpoint.

The anteroposterior diameters of the VFG and host bone were measured on plain radiographs at the point of greatest thickness of the graft (A) and at the point nearest the proximal graft-host junction (B), respectively, immediately after surgery and at follow-up. Graft hypertrophy was determined using the formula described by de Boer and Wood (Fig. 2) [11].

$$Hypertrophy\ (\%) = \frac{\frac{A2}{B2} - \frac{A1}{B1}}{\frac{A1}{B1}} \times 100$$

Lateral radiographs were not used in the measurements because implant overlap compromised measurement reliability. Hypertrophy was considered significant if the hypertrophy index increased by >20%. For a biologically active graft, a hypertrophy index of 0–20% indicated the absence of significant hypertrophy, whereas an atrophic graft was defined as an index <0%. Graft

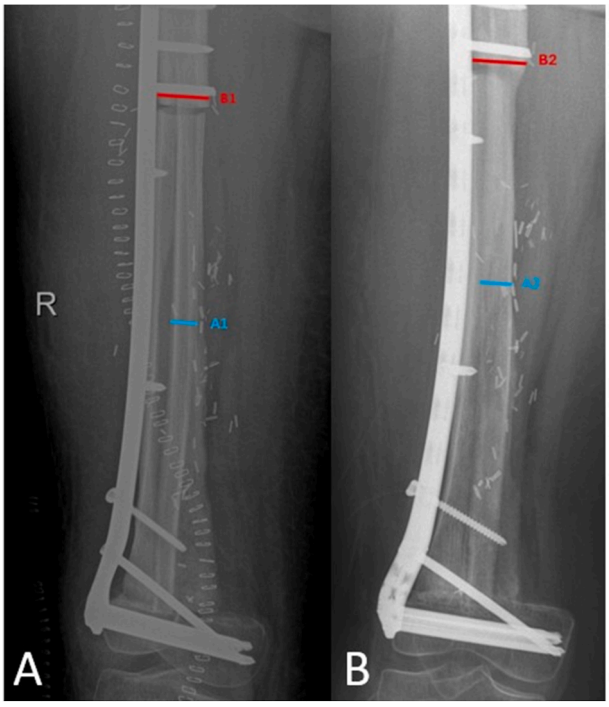


Fig. 2. An example of the measurements made in order to calculate hypertrophy. A: Immediate postoperative and (B) 6th month follow-up plain radiographs.

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viability was assessed on serial radiographs based on continuation of hypertrophy and the absence of progressive graft osteolysis. Contrast-enhanced MRI signal characteristics may provide adjunct information on flap viability; however, this was not used as the primary viability classifier in this study [12].

Functional outcomes: The Musculoskeletal Tumor Society (MSTS) score was used to assess functional outcomes. This score ranges from 0 to 30, and includes factors such as function, pain, emotional acceptance, use of assistive devices, walking ability, and abnormal gait [13].

Survival outcomes: Local recurrence, distant metastasis, and mortality were evaluated for oncological events. Overall survival, metastasis-free survival, and recurrence-free survival rates were ascertained. Survivorship status and date of death were determined from hospital records and, when available, national registry information.

Complications: Complications were divided into clinical and radiological. Clinical complications were classified as wound problems, deep infection, and hematoma, and radiological complications were classified as nonunion, stress fracture, pathological fracture, host bone fracture, or implant failure. Patients who underwent reoperation because of complications were also evaluated. Complications were additionally graded using the Clavien–Dindo classification; events requiring surgical, endoscopic, or radiologic intervention (grade III or higher) were considered major complications and corresponded to cases requiring reoperation. In addition, cases in which the implant does not break but detaches from its position are also included in the implant failure group. Host bone fractures are defined as fractures occurring at any point in surgically treated bone, with the exception of the graft. Stress fractures are defined as fractures occurring in any of the cortices of the graft bone that are not supported by an implant. Pathological fractures are defined as host bone or graft fractures that occur as a result of recurrence or relapse of the patient's primary malignancy. Nonunion was defined as the absence of radiographic union (i.e., consolidation of fewer than three of four cortices) at either the proximal or distal graft–host junctions by the end of the 12th postoperative month, as observed on both anteroposterior and lateral radiographs.

Statistical analysis: Analyses were performed using IBM SPSS Statistics version 29.0 (IBM Corp., Armonk, NY, USA). Continuous variables are presented as mean ± standard deviation (range) and were assessed for normality using the Shapiro–Wilk test. Between-group comparisons were performed with Student's t test for normally distributed variables and the Mann–Whitney U test for non-normally distributed variables. Categorical variables were compared using Pearson's chi-square test, Fisher's exact test, or the Fisher-Freeman-Halton test, as appropriate. Survival outcomes were analyzed using the Kaplan–Meier method. In lower-extremity reconstructions, univariable associations with nonunion at 12 months were evaluated using chi-square or Fisher's exact tests, and multivariable logistic regression was performed to assess age, sex, diagnosis group, preoperative radiotherapy, and neoadjuvant/adjuvant chemotherapy as potential predictors. Logistic regression results are reported as odds ratios with 95% confidence intervals. Statistical significance was set at $p < 0.05$.

3. . Results

The study included 127 patients with a mean age of 16.6 ± 11.3 years (range, 2–66 years). Demographic characteristics are shown in Table 1. Osteosarcoma and Ewing sarcoma were the most common diagnoses, and the femur and tibia were the most frequently affected sites. Wound problems occurred in 32 patients, deep infection in 6, and hematoma/seroma in 15. Mean graft hypertrophy was 16.1 ± 11.6% (range, −17 to 77) at 3 months, 29.8 ± 17.8% (range, −20 to 93) at 6 months, and 46.2 ± 28.0% (range, −34 to 142) at 12 months. Hypertrophy at 6 and 12 months was significantly greater than at 3 months (both $p < 0.001$), and hypertrophy at 12 months was significantly greater than at 6 months ($p < 0.001$). Overall clinical and radiological outcomes are summarized in Table 2. In lower-extremity reconstructions with available data ($n = 79$), time to full weight bearing was 14.2 ± 7.7 months (range, 4–40 months). At last follow-up, 3 patients required a walking aid, and the remaining patients were able to walk unaided.

Neoadjuvant CT was administered to 100 patients (78.7%) and adjuvant CT to 106 patients (83.5%). Preoperative RT was delivered to 31 patients (24.4%) and postoperative RT to 9 patients (7.1%); 5 patients received both preoperative and postoperative RT. Treatment exposure by diagnosis is summarized in Supplementary Table S2. Among the 65 osteosarcoma patients in this cohort, 8 (12.3%) received preoperative RT and 57 (87.7%) did not. Osteosarcoma was the most common diagnosis among patients who did not receive preoperative RT (57/96, 59.4%), whereas Ewing sarcoma was the most common diagnosis in the preoperative RT group (19/31, 61.3%; $p = 0.008$). Postoperative RT was more frequently used in patients who also received preoperative RT (6/31, 19.4%) than in those without preoperative RT (3/96, 3.1%; $p = 0.007$). CT exposure did not differ significantly between patients with and without preoperative RT.

Compared with patients who did not receive preoperative RT, those who received preoperative RT had no significant differences in wound problems, deep infection, hematoma/seroma, reoperation, time to initial or complete union, or nonunion at 12 months. In contrast, mean graft hypertrophy was significantly lower in the preoperative RT group at 3 and 6 months ($p = 0.013$ and $p = 0.005$, respectively), whereas the between-group difference was not statistically significant at 12 months. In lower-extremity reconstructions with available data, time to full weight bearing was 13.2 ± 6.3 months in patients without preoperative RT and 20.5 ± 12.6 months in those with preoperative RT; this difference was not statistically significant ($p = 0.120$). In the subset with paired radiographic and functional timing data ($n = 73$), 28 patients (38.4%) achieved full weight bearing before radiographic complete union at both junctions, whereas only 2 patients (2.7%) achieved full weight bearing before initial union at either junction (Supplementary Table S3).

A subsequent comparison of the lower extremity and upper extremity results revealed no significant disparities in time to initial or complete union and hypertrophy metrics (Table 3). However, nonunion at 12 months was observed only in lower-extremity reconstructions ($p = 0.048$). Although there was no significant difference, graft hypertrophy was consistently higher in the lower extremity than in the upper extremity at 3, 6, and 12 months. Graft hypertrophy values were numerically higher in the group that did not receive preoperative RT, both in the lower extremity (Table 4) and the upper extremity (Table 5). However, these differences were not statistically significant.

In multivariable logistic regression limited to lower-extremity reconstructions (Table 6), preoperative radiotherapy was not an independent predictor of nonunion at 12 months (OR 2.03, 95% CI 0.48–8.48; $p = 0.334$). Male sex was associated with lower odds of nonunion, while age, diagnosis group, and chemotherapy variables were not significantly associated with nonunion. Univariable analyses are presented in Supplementary Table S4 and showed that deep infection and implant fracture were associated with nonunion, while wound problems showed a borderline association. Overall, nonunion appeared to be multifactorial.

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Table-1
Demographic data of patients.

Patients treated with Vascularized Fibula Graft (n = 127)	
Age, years (Mean ± SD, Min-Max)	16.6 ± 11.3, 2–66
Gender, Female/Male	62/65
Side Right/Left	66/61
Diagnosis	
Osteosarcoma	65 (51.2%)
Ewing sarcoma	40 (31.5%)
Malign mesenchymal tumor	12 (9.4%)
Fibrous dysplasia	3 (2.4%)
Chondrosarcoma	3 (2.4%)
Adamantinoma	2 (1.6%)
Giant cell bone tumor	2 (1.6%)
Extremity	
Femur	62 (48.8%)
Tibia	44 (34.6%)
Humerus	15 (11.8%)
Ulna	1 (0.8%)
Radius	2 (1.6%)
Foot	3 (2.4%)
Chemotherapy	
Neo-adjuvant, Yes/No	100 (78.7%)/27 (21.3%)
Adjuvant, Yes/No	106 (83.5%)/21(16.5%)
Radiation therapy	
Neo-adjuvant, Yes/No	31 (24.4%)/96(75.6%)
Adjuvant, Yes/No	9 (7.1%)/118(92.9%)

Table-2
Overall clinical and radiological results of all patients.

Patients treated with Vascularized Fibula Graft (n = 127)	Mean ± SD	Min – Max
Wound problem, Yes/No	32/95	
Deep infection, Yes/No	6/121	
Hematoma, Yes/No	15/112	
Initial bony union time, months	5.6 ± 2.1	1–16
Total union time, months	11.3 ± 3.2	5–24
Nonunion, Yes/No	20/107	
Pathological fracture, Yes/No	3/124	
Stress fracture, Yes/No	12/115	
Host bone fracture, Yes/No	2/125	
Implant fracture, Yes/No	7/120	
Third month hypertrophy	16.1 ± 11.6	−17–77
-Atrophic graft, n (%)	4 (3.1%)	
-Absence of significant hypertrophy,	83 (65.4%)	
-Significant hypertrophy	40 (31.5%)	
Sixth month hypertrophy	29.8 ± 17.8	−20–93
-Atrophic graft n (%)	4 (3.1%)	
-Absence of significant hypertrophy	34 (26.8%)	
-Significant hypertrophy	89 (70.1%)	
Twelfth month hypertrophy	46.2 ± 28	−34–142
-Atrophic graft, n (%)	4 (3.1%)	
-Absence of significant hypertrophy	16 (12.4%)	
-Significant hypertrophy	107 (84.3%)	
Reoperation (Clavien–Dindo ≥ III), Yes/No	20/107	
Vascular viability, Yes/No	122/5	

In an exploratory subgroup analysis within the preoperative RT cohort, hypertrophy values tended to be lower in Ewing sarcoma compared with osteosarcoma at 3 and 6 months, but the differences did not reach statistical significance ($p = 0.095$ for both comparisons).

Loss of vascular viability was observed in 5/127 patients. Of these, 4 were in the lower extremity and 1 was in the upper extremity ($p = 0.703$). Four of the 5 patients without vascular viability did not receive preoperative RT, whereas 1 received preoperative RT ($p = 0.815$).

Local recurrence developed in 13 (10.2%) patients and distant metastasis in 24 (18.9%) patients, while 14 (11.0%) died of the disease during follow-up. Local recurrence-free survival rates were 91.4% and 89.8%, metastasis-free survival rates were 83.5% and 81.9%, and overall survival rates were 89.8% and 89.0% at 5 and 10 years, respectively. The average follow-up period was 69 ± 51 months (range, 15–262 months). Although the inclusion criterion required ≥12 months of follow-up, the minimum observed follow-up in this cohort was 15 months. The average MSTS score was 24.2 ± 5.4 (range, 2–30) at final follow-up.

Local recurrence was observed in 2/8 osteosarcoma patients with preoperative RT and 6/57 without ($p = 0.243$). Metastasis occurred in 1/8 osteosarcoma patients with preoperative RT and 15/57 without ($p = 0.396$). In Ewing sarcoma, local recurrence occurred in 2/19 patients with preoperative RT and 0/21 without ($p = 0.127$). Metastasis occurred in 2/19 Ewing sarcoma patients with preoperative RT and 3/21 without ($p = 0.720$).

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Table-3
Comparison of demographic and radiological results between the upper and lower extremity tumors.

	Lower extremity tumors treated with VFG (n = 109)		Upper Extremity tumors treated with VFG (n = 18)		p value
	Mean ± SD	Min – Max	Mean ± SD	Min – Max	
Age, years	16.8 ± 11.4	4–66	15.3 ± 10.5	2–42	0.60
Gender, Female/Male	55/54		7/11		0.363
Side, Right/Left	56/53		10/8		0.742
Diagnosis					
Osteosarcoma	59		6		0.388
Ewing sarcoma	32		8		
Malign mesenchymal	10		2		
Fibrous dysplasia	2		1		
Chondrosarcoma	3		0		
Adamantinoma	2		0		
Giant cell bone tumor	1		1		
Extremity					
Femur	62		–		
Tibia	44		–		
Humerus	–		15		
Ulna	–		1		
Radius	–		2		
Foot	3		–		
Preoperative radiotherapy, Yes/No	21/88		10/8		<0.001[a]
Postoperative radiotherapy, Yes/No	6/103		3/15		0.087
Preoperative chemotherapy, Yes/No	86/23		14/4		0.914
Postoperative chemotherapy, Yes/No	93/16		13/5		0.166
Wound problem, Yes/No	29/80		3/15		0.368
Deep infection, Yes/No	5/104		1/17		0.858
Hematoma, Yes/No	14/95		1/17		0.375
Initial bony union time, months	5.79 ± 2.1	1–16	4.8 ± 1.8	3–9	0.088
Total union time, months	11.4 ± 3.2	5–24	10.6 ± 2.8	6–16	0.413
Nonunion, Yes/No	20/89		0/18		0.048[a]
Pathological fracture, Yes/No	3/106		0/18		0.476
Stress fracture, Yes/No	12/97		0/18		0.139
Host bone fracture, Yes/No	2/107		0/18		0.562
Implant fracture, Yes/No	7/102		0/18		0.269
3-month hypertrophy, %	16.76 ± 11.7	−17–77	12.44 ± 11.06	−14–28	0.147
-Atrophic graft	2		2		0.112
-Absence of significant hypertrophy	72		11		
-Significant hypertrophy	35		5		
6-month hypertrophy, %	30.8 ± 18.2	−20–93	23.6 ± 14.7	2–51	0.113
-Atrophic graft	2		2		0.107
-Absence of significant hypertrophy	29		5		
-Significant hypertrophy	78		11		
12-month hypertrophy, %	47.88 ± 29.1	−34–142	36.1 ± 18	5–76	0.101
-Atrophic graft	2		3		0.088
-Absence of significant hypertrophy	13		3		
-Significant hypertrophy	94		13		
Reoperation (Clavien–Dindo ≥ III), Yes/No	18/91		2/16		0.560
Vascular viability, Yes/No	105/4		17/1		0.703
Using walking aids, Yes/No	3/103		0/18		0.509

VFG = Vascularized Fibula Graft.
[a] Statistically significant.

4. . Discussion

VFGs have become common alternatives to massive allografts and the mainstay of biological reconstruction in orthopaedic oncology. Even with VFGs, bone healing can be compromised. We compared graft union and hypertrophy in patients with bone tumors who underwent extensive resection with VFG with and without preoperative RT. Preoperative RT had no significant effect on initial or complete union time, and no difference was found in nonunion compared with the non-RT group. However, patients receiving preoperative RT had less hypertrophy at the 3rd and 6th months, with no difference at the 12th month. Time to union and hypertrophy showed no significant differences between lower and upper extremity reconstructions, although nonunion occurred only in the lower extremity. Postoperative RT was used in selected cases based on multidisciplinary oncologic indications (*e.g.*, local control strategy in radiosensitive tumors or high-risk features), despite negative margins. Mericli et al. investigated graft failure in 55 patients with 60 VFGs [14]. Eight patients received preoperative RT, with no correlation between RT and graft healing, but a significant correlation between graft failure and nonunion. Claxton et al. reported on patients who underwent VFG for radiation-related fracture nonunion in the upper extremity (mean radiation dose 41.3 Gy, administered 11 years prior to surgery) [15]. First-time union rate was 71%, but after repeat grafting, all patients healed, with median union time of 10 months. Gottsauner et al. evaluated 100 jaw reconstruction cases for ossification between bone segments using radiographs to assess preoperative RT effects [16]. Ossification rates in preoperative (447 ± 136 days) and postoperative (510 ± 112 days) radiation groups showed no difference. The control group showed fastest ossification at 304 ± 37 days, indicating irradiation compromises jaw reconstruction ossification. Shahzad et al. performed femoral reconstruction with intercalar-metal prosthesis and fibular free flap in 8 patients and

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Table-4
Comparison of demographic and radiological results between the lower extremity groups.

	Patients without preoperative radiation therapy (n = 88)		Patients with preoperative radiation therapy (n = 21)		p value
	Mean ± SD	Min – Max	Mean ± SD	Min – Max	
Age, years	15.3 ± 9.6	4–44	22.9 ± 16.1	5–66	0.006
Gender, Female/Male	46/42		9/12		0.438
Side, Right/Left	48/40		8/13		0.175
Diagnosis					
Osteosarcoma	53		6		0.025[a]
Ewing sarcoma	19		13		
Malign mesenchymal	8		2		
Fibrous dysplasia	2		0		
Chondrosarcoma	3		0		
Adamantinoma	2		0		
Giant cell bone tumor	1		0		
Postoperative radiotherapy, Yes/No	2/86		4/17		0.002[a]
Preoperative chemotherapy, Yes/No	68/20		18/3		0.394
Postoperative chemotherapy, Yes/No	73/15		20/1		0.153
Wound problem, Yes/No	25/63		4/17		0.383
Deep infection, Yes/No	4/84		1/20		0.966
Hematoma, Yes/No	11/77		3/18		0.826
Initial bony union time, months	5.83 ± 2.13	2–16	5.5 ± 2.3	1–9	0.641
Total union time, months	11.41 ± 3.2	5–24	11.31 ± 3.4	5–16	0.906
Nonunion, Yes/No	15/73		5/16		0.472
Pathological fracture, Yes/No	3/85		0/21		0.391
Stress fracture, Yes/No	12/76		0/21		0.073
Host bone fracture, Yes/No	2/86		0/21		0.486
Implant fracture, Yes/No	6/82		1/20		0.730
3-month hypertrophy, %	17.63 ± 12.3	−17–77	12.95 ± 8.2	0–31	0.082
-Atrophic graft	1		1		0.223
-Absence of significant hypertrophy	56		16		
-Significant hypertrophy	31		4		
6-month hypertrophy, %	32.29 ± 18.7	−20–93	24.6 ± 14.4	0–55	0.060
-Atrophic graft	1		1		0.196
-Absence of significant hypertrophy	21		8		
-Significant hypertrophy	66		12		
12-month hypertrophy, %	49.23 ± 30.2	−34–142	42.23 ± 23.4	9–92	0.324
-Atrophic graft	1		1		0.511
-Absence of significant hypertrophy	11		2		
-Significant hypertrophy	76		18		
Reoperation (Clavien–Dindo ≥ III), Yes/No	13/75		5/16		0.316

[a] Statistically significant.

allograft and fibular free flap in 16 patients [17]. Complications occurred in 2 prosthesis patients and 13 allograft-free fibula patients, with rates unaffected by CT or RT. Taken together, these findings suggest that preoperative RT may impair early graft hypertrophy without compromising ultimate union or graft survival after VFG reconstruction.

Nonunion at 12 months was observed in 20 patients (15.7%) and occurred exclusively in lower-extremity reconstructions, consistent with the higher mechanical demands of weight-bearing segments. Nonunion after VFG reconstruction is likely multifactorial, reflecting the combined effects of mechanical stability (fixation strength, graft-host contact/compression, alignment, and early loading), defect characteristics, and biologic factors. Postoperative complications such as wound problems and infection can compromise local healing and may contribute to delayed union or nonunion in complex oncologic reconstructions. This interpretation was supported by univariable analyses, in which deep infection and implant fracture were associated with nonunion, whereas wound problems showed a borderline association. Implant fracture likely reflects mechanical failure in the setting of impaired healing rather than a baseline predictor. Although adjuvant therapies may influence remodeling, our multivariable analysis did not identify preoperative radiotherapy as an independent predictor of nonunion, suggesting that mechanical and complication-related factors may be more influential. Previous extremity VFG series have similarly reported nonunion and junctional problems as major drivers of secondary procedures and graft failure, underscoring the importance of robust fixation and meticulous management of soft tissue and infection risk [6,14].

Radiation-induced damage to soft tissue and vascular structures is a multistep process that begins with ionization events and free radical generation, which directly damage vital cellular structures such as the endothelial lining of blood vessels. The subsequent excessive collagen deposition culminates in fibrosis, tissue retraction, and atrophy over time, with the reduced blood supply further exacerbating the injury in a vicious cycle of inflammation and chronic fibrotic repair [18]. Radiation therapy will also have adverse effects on small blood vessels in microsurgery. Histologic observations of irradiated vessels displayed more abnormalities, which included diminished smooth muscle density, endothelial cell dehiscence, and vessel wall fibrosis. In a recent systematic review and meta-analysis, Tasch et al. identified that microvascular surgery on irradiated vessels is associated with a heightened risk of thrombosis, attributed to preexisting damage to the vessel walls. The study further elucidated that radiation detrimentally affects the vascular endothelium, promoting proadhesive and prothrombotic characteristics, which result in abnormal coagulation and fibrinolysis. Additionally, the research highlighted that preoperative RT correlates with an increased likelihood of both total and partial free flap failure [19]. This contradicts our results, which showed no significant difference in

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Table-5
Comparison of demographic and radiological results between the upper extremity groups.

	Patients without preoperative radiation therapy (n = 8)		Patients with preoperative radiation therapy (n = 10)		p value
	Mean ± SD	Min – Max	Mean ± SD	Min – Max	
Age, years	16.1 ± 5.6	9–25	14.6 ± 13.6	2–42	0.766
Gender, Female/Male	5/3		2/8		0.066
Side, Right/Left	2/6		8/2		0.020[a]
Diagnosis					
Osteosarcoma	4		2		0.163
Ewing sarcoma	2		6		
Malign mesenchymal	0		2		
Fibrous dysplasia	1		0		
Chondrosarcoma	0		0		
Adamantinoma	0		0		
Giant cell bone tumor	1		0		
Postoperative radiotherapy, Yes/No	1/7		2/8		0.671
Preoperative chemotherapy, Yes/No	5/3		9/1		0.163
Postoperative chemotherapy, Yes/No	5/3		8/2		0.410
Wound problem, Yes/No	2/6		1/9		0.396
Deep infection, Yes/No	0/8		1/9		0.357
Hematoma, Yes/No	1/7		0/10		0.250
Initial bony union time, months	4.14 ± 1.4	3–6	5.33 ± 2	3–9	0.208
Total union time, months	9.85 ± 2.8	6–12	11.33 ± 2.82	6–16	0.320
Nonunion, Yes/No	0/8		0/10		1.000
Pathological fracture, Yes/No	0/8		0/10		1.000
Stress fracture, Yes/No	0/8		0/10		1.000
Host bone fracture, Yes/No	0/8		0/10		1.000
Implant fracture, Yes/No	0/8		0/10		1.000
3-month hypertrophy, %	15.2 ± 8.1	5–26	10.2 ± 12.9	−14–28	0.351
-Atrophic graft	0		2		0.351
-Absence of significant hypertrophy	5		3		
-Significant hypertrophy	3		2		
6-month hypertrophy, %	29.62 ± 14.8	9–51	24.6 ± 13.3	2–54	0.124
-Atrophic graft	0		2		0.351
-Absence of significant hypertrophy	2		3		
-Significant hypertrophy	6		5		
12-month hypertrophy, %	39.62 ± 20.2	13–76	33.4 ± 17.1	5–92	0.490
-Atrophic graft	0		2		0.330
-Absence of significant hypertrophy	2		1		
-Significant hypertrophy	6		7		
Reoperation (Clavien–Dindo ≥ III), Yes/No	2/6		0/10		0.094

[a] Statistically significant.

Table-6
Multivariable logistic regression for nonunion at 12 months in lower extremity reconstructions.

	Patients treated with Vascularized Fibula Graft for lower extremity bone tumors (n = 109)		
Variable	*OR*	*95% CI*	*p value*
Age (per year)	1.01	0.96–1.07	0.659
Male (vs female)	0.23	0.07–0.72	0.012
Preoperative radiotherapy (yes vs no)	2.03	0.48–8.48	0.334
Neoadjuvant chemotherapy (yes vs no)	1.95	0.33–11.62	0.466
Adjuvant chemotherapy (yes vs no)	0.87	0.13–5.97	0.891
Diagnosis: Ewing sarcoma (vs osteosarcoma)	0.49	0.13–1.84	0.290
Diagnosis: Other (vs osteosarcoma)	0.80	0.11–5.58	0.822

OR = odds ratio; CI = confidence interval.
Model fit (Hosmer–Lemeshow): p = 0.936.

hypertrophy at 12 months, however only a single study by Verhelst et al. was included involving VFGs in this systematic review and meta-analysis. That study found that patients who underwent pre- or postoperative CT or RT did not have higher failure rates [20]. These findings also align with our results even though it has been conducted in a different region of the body. Tall et al. showed that previous RT is a risk factor for head and neck free flap failure, especially in delayed reconstructions. They have suggested that this may be linked to previous findings of impaired fibrinolysis in irradiated microvascular recipient veins, which is further supported by the beneficial effect of tPA during salvage surgery [21]. In our study, patients who received preoperative RT had less hypertrophy at 3 and 6 months, but there was no significant difference at 12 months. Based on the results of this article, the reduction in early hypertrophy may be explained by impaired fibrinolysis and resultant thrombosis.

A practical concern is the reliability of microvascular anastomosis in irradiated fields. Prior studies have shown that microvascular reconstruction can be performed in irradiated recipient sites, although fibrosis and vascular changes may increase technical difficulty and the risk of complications [19,21]. In our cohort, recipient vessels used for anastomosis were within the radiotherapy field in all irradiated patients, yet graft viability remained high.

Postoperative monitoring of VFGs to detect early vascular compromise is pivotal for graft success. A range of monitoring techniques has been described, including serial clinical examination, handheld or implantable Doppler monitoring, spectroscopy/near-infrared methods, fluorescence angiography, and other adjunctive technologies; however, clinical monitoring alone remains highly effective, and it has been difficult to demonstrate consistently superior flap survival with alternative modalities [22–24]. In our practice, early postoperative monitoring relied primarily on frequent clinical assessment of the soft-tissue

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envelope (e.g., color, temperature, turgor, and capillary refill), with particular emphasis on the first 48 h, which is considered the most critical window for timely detection and successful salvage of vascular compromise [24,25]. Doppler ultrasonography can provide real-time flow information but is operator-dependent and may be technically challenging adjacent to bone and fixation hardware; therefore, it was not used routinely in our cohort. Beyond the immediate postoperative period, serial anteroposterior and lateral radiographs were obtained at regular intervals and were used as the primary method to assess graft viability, based on continuation of graft hypertrophy and absence of progressive osteolysis. Using these criteria, 5/127 patients exhibited loss of graft viability; 4 were in the lower extremity and 1 was in the upper extremity ($p = 0.703$). Four of the five patients without graft viability did not receive preoperative RT, whereas one received preoperative RT ($p = 0.815$).

This study had several limitations. The retrospective design and treatment heterogeneity across a long study period may have introduced confounding. Although diagnosis-specific institutional RT protocols were used, patient-level dosimetry and detailed field parameters were not available for dose–response analyses. Surgeons with different experience levels may have affected complication rates, and some complications (e.g., neurological deficits) were not systematically captured. The viability of VFG was not monitored by further radiological evaluation such as positron emission tomography.

5. . Conclusion

The use of preoperative RT did not result in a notable impact on the time required for union or the incidence of nonunion in patients undergoing VFG reconstruction following wide resection of bone tumors. However, it led to reduced graft hypertrophy at early time points (3 and 6 months), with no statistically significant difference by 12 months. These findings support the use of preoperative RT when required for oncologic local control, especially in cases where tumors are situated in close proximity to and are invasive towards major neurovascular structures, without adversely affecting graft union or viability.

Ethical statement

This retrospective study was approved by the local Institutional Review Board/Ethics Committee. All procedures were performed in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments. Written informed consent was obtained from all patients and/or their legal guardians.

Ethical review committee statement

This study was approved by the institutional review boards of our university medical faculty hospital (26.06.2024). Informed consent was obtained from all.

This study was performed in Istanbul University Faculty of Medicine.

Consent for publication

Participants agree to the publication of information about them.

Data availability statement

The data of study will be made available on reasonable request.

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Conflict of interest statement

The authors declare that they have no conflict of interest.

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Appendix A. Supplementary data

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