Site-dependent Replacement or Internal Fixation for Postradiation Femur Fractures After Soft Tissue Sarcoma Resection

Han Jo Kim MD, John H. Healey MD,
Carol D. Morris MD, Patrick J. Boland MD

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Abstract

Background High-dose radiation retards bone healing, compromising the surgical results of radiation-induced fractures. Prosthetic replacement has traditionally been reserved as a salvage option but may best achieve the clinical goals of eliminating pain, restoring function and avoiding complications.

Questions/purposes We asked whether patients undergoing prosthetic replacement at index surgery for radiation-related subtrochanteric or diaphyseal fractures of the femur had fewer complications than those undergoing open reduction internal fixation at index operation.

Methods We retrospectively reviewed records from 1045 patients with soft tissue sarcomas treated with surgical resection and high-dose radiation therapy between 1982 and 2009 and identified 37 patients with 39 fractures. We recorded patient demographics, diagnosis, type of surgical resection, total radiation dose, fracture location and pattern,

years after radiation the fracture occurred, type of surgical fixation, and associated complications.

Results Patients undergoing prosthetic replacement at index surgery had a lower number of major complications and revision surgeries than those undergoing index open reduction internal fixation. Patients undergoing open reduction internal fixation at index surgery had a nonunion rate of 63% (19 of 30). Fractures located in the metaphysis were more likely to heal than those located in the subtrochanteric or diaphyseal regions.

Conclusions Radiation-induced fractures have poor healing potential. Our data suggest an aggressive approach to fracture treatment with a prosthetic replacement can minimize complications and the need for revision surgery.

Level of Evidence Level III, therapeutic study. See Guidelines for Authors for a complete description of levels of evidence.

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Each author certifies that his or her institution approved the human protocol for this investigation that all investigations were conducted in conformity with ethical principles of research, and that informed consent for participation in the study was obtained.

This work was performed at Memorial Sloan-Kettering Cancer Center.

H. J. Kim (✉)

Department of Orthopaedic Surgery, Hospital for Special Surgery, 535 East 70th Street, New York, NY 10021, USA
e-mail: hanjokimmd@gmail.com

J. H. Healey, C. D. Morris, P. J. Boland
Department of Surgery, Orthopaedic Service, Memorial Sloan-Kettering Cancer Center, New York, NY, USA

Introduction

External beam radiation therapy is an effective tool for decreasing the rate of local recurrence of soft tissue sarcomas. However, its use is not without substantial complications [1]. Radiation-induced complications have been described in the literature previously and include fractures (6%–25%), delayed bone healing (> 45%), osteonecrosis (15%), wound-healing complications (10%–28%), and in cases of the skeletally immature, growth plate arrest (60%) [1, 13, 14, 17, 19, 21].

The effects of radiation on bone have been attributed to the impaired proliferation of normal functioning osteoblasts, as well as its effects on neoangiogenesis in fracture healing [6, 7, 17, 18]. Furthermore, soft tissue sarcoma resection poses other potential adverse effects on bone.

Circumferential resection or wide excision is often needed to ensure clear margins during limb salvage surgery for soft tissue sarcomas, especially in the thigh. Several studies suggest periosteal stripping associated with soft tissue sarcoma resection is also associated with high rates of pathologic fractures [12, 13]. These fractures create major problems for the patient, not only because of their decreased propensity to heal, but also because of the potential complications associated with wound healing of postirradiated tissues.

Numerous reports describe treatment alternatives for these fractures, including primary open reduction and internal fixation (ORIF) [2, 9], prophylactic fixation [2, 8], ORIF with vascularized bone grafts [7], and prosthetic replacements [2, 12]. Regardless of treatment approach, these studies all reflect that treatment of these fractures is challenging and has a substantial failure rate. A consensus on the optimal approach to successful treatment is difficult to achieve because of the paucity of patients with radiation-induced fractures. In addition, it is unclear whether the location should influence the type fracture fixation and whether location influences complication rates.

We determined whether the primary method of treatment (ie, casting, ORIF, prosthetic replacement) altered (1) the rate of complications and (2) need for revision surgery. We further asked (3) whether patients who had prosthetic replacement as their index operation had fewer complications and revision surgeries after sustaining a fracture after soft tissue sarcoma resection and radiation.

Patients and Methods

We retrospectively identified 1045 patients who met the ICD-9 Code search criteria for radiation therapy and soft tissue sarcoma and fractures from 1982 to 2008. We used computer-based hospital charts, including all clinics, office, and operative notes, to gather information on patient demographics, diagnosis, surgery type, total radiation dose, years after radiation the fracture occurred, fracture pattern and location, and associated complications. We defined a major complication as one requiring revision surgery for a previously treated fracture, nonunion, malunion, broken hardware, or infection. A minor complication was one that resolved without surgical intervention, such as superficial wound infections that resolved with oral antibiotics.

Patients qualified for the study if their fractures were associated with minimal or no trauma and if the fracture was within the field of previous radiation therapy. During this time, 37 patients (22 women, 15 men; average age, 62.5 years) with 39 fractures had surgery for a radiation-induced fracture after soft tissue sarcoma resection, indicating an incidence of 3.6% (37 of 1045) (Table 1). The

Table 1. General characteristics of the patients (n = 37) and their fractures (n = 39)

Characteristic	Value
Age (years)*	62.5 ± 11.5
Gender (male:female)	15:22
Diagnosis	
Liposarcoma	13
Angiosarcoma	4
Fibrosarcoma	1
Myofibrosarcoma	1
Spindle cell sarcoma	1
Malignant fibrous histiocytoma	10
Synovial sarcoma	2
Leiomyosarcoma	1
Myxoliposarcoma	1
Lymphoma	2
Other	1
Fracture location	
Metaphyseal	6
Diaphyseal	33
Fracture pattern	
Displaced	11
Nondisplaced	28
Initial management	
Open reduction internal fixation	30
Prophylactic nailing	1
Prosthetic replacement	6
Closed reduction (casting/brace)	2
Tumor size (cm)*	12.41 ± 5.46
Tumor grade (AJCC grading system)	
High	34
Low	5
Periosteal stripping	
Yes	29
No	10
Time after radiation fracture occurred (years)*	3.46 ± 2.90
Total radiation dose (cGy)*	5926.11 ± 887.42
Complications	
Total	26
Nonunion	18
Broken hardware	3
Osteomyelitis	2
Wound infection	3

* Values are expressed as mean ± SD; AJCC = American Joint Committee on Cancer.

two additional fractures were in patients who initially underwent ORIF and had fractures below the construct in the same bone more than 5 years after the initial fracture (dynamic hip screw for an initial intertrochanteric fracture that then fractured below the distal end of the plate;

Fig. 1 A flowchart illustrates the classification of our patients and fractures for data analysis.

intramedullary nail for a subtrochanteric fracture that developed a fracture at the distal interlock screw). Since the number of patients differed from the number of fractures, throughout the remainder of the article, we will refer to the number of fractures rather than patients to avoid confusion (Fig. 1). Fractures were treated based on location and type and therefore allowed for more meaningful interpretation of outcome variables. The mean time to fracture was 3.5 years after radiation, and the average radiation dose was 5926.11 Gy (range, 1500–6660 Gy). Minimum followup was 1.1 years (average, 12.2 years; range, 1.1–19.5 years). Tumor grading was based on the American Joint Committee on Cancer grading system [3]; this system is based the size, depth, nodal seeding, presence of metastases, and histopathologic grade of the soft tissue sarcoma. No patients were lost to followup.

Fracture patterns were categorized as either nondisplaced or displaced fractures. A nondisplaced fracture did not extend through both cortical silhouettes on two radiographic views, while displaced fractures extended through both cortices. We did not quantify the distance of displacement or angulation at the fracture site. Fracture location was categorized into diaphyseal or metaphyseal. Subtrochanteric fractures were considered diaphyseal fractures.

Of the 39 fractures, six underwent prosthetic replacement at index surgery, while 33 fractures underwent other methods of treatment. Of the 33 fractures, 30 underwent ORIF for treatment of their fracture. Of the remaining three fractures, one fracture was treated with prophylactic nailing at the time of resection, and two were treated with a cast (Fig. 1) and therefore were excluded from our data analysis. In the ORIF group, 11 had intramedullary nailing and 19 plate and screw fixation at index operation. There were no differences in demographic information between the two groups (Table 2).

All patients had wide resections with or without periosteal stripping for their initial sarcoma resection. Resection was considered wide when all margins of the

Table 2. Differences between patients with ORIF and patients with prosthetic replacement at index surgery

Characteristic	ORIF (n = 30)	Prosthetic replacement (n = 6)	P value
Age (years)*	63.5	56.3	
Gender (male:female)	11:19	4:2	0.18
Fracture location			0.003
Metaphyseal	4	4	
Diaphyseal	26	2	
Fracture pattern			0.62
Displaced	22	5	
Nondisplaced	8	1	
Number of surgeries*	2.3	1.2	0.03
Tumor size (cm)*	12.3	12.2	0.97
Tumor grade (AJCC grading system)			0.84
High	26	5	
Low	4	1	
Periosteal stripping			0.75
Yes	22	4	
No	8	2	
Time after radiation fracture occurred (years)*	3.21	4.90	0.59
Total radiation dose (cGy)*	5871.79	6120.00	0.58
Complications*	1.96	0.17	0.007

* Values are expressed as means; ORIF = open reduction internal fixation; AJCC = American Joint Committee on Cancer.

excised specimens were free of tumor. This was determined by examining the ink marked borders of the excised specimens. No patients had positive margins as defined by ink at the margin.

Postoperatively, all patients had drains after surgery. Drains were removed once the drainage had decreased to less than 30 mL per 24-hour period, and all patients were mobilized with physical therapy on the first postoperative day. All patients were followed up at 2 weeks for a wound evaluation. Then, patients in the ORIF group were followed with serial radiographs every 4 to 6 weeks to assess healing. Once healing was verified radiographically and the patient was doing well, followup progressed to every 3 to 6 months and annual followups thereafter. Patients who underwent prosthetic replacement underwent followup at 4 to 6 weeks with new radiographs to assess component alignment and then followup progressed to every 3 to 6 months with radiographs on an annual basis. Our followup protocol was according to National Comprehensive Cancer Network guidelines [15].

Subsequent radiation therapy was delivered to the patients in a uniform fractionation protocol by the radiation oncologists at our institution.

A delayed union was considered to occur if there were no radiographic signs of healing at 6 months and subsequent healing occurred without further surgical intervention [13]. A nonunion was considered present if osseous union did not occur before 8 months. Sometimes a nonunion was present with fatigue failure of hardware (ie, broken instrumentation), progressive deformity, and/or pain. Additional surgery was necessary in all these situations to address the nonunion due to the patients' inability to ambulate.

Patient demographic information and information about diagnosis, location of tumor, and presence of major complications were designated categorical variables compared between the groups undergoing ORIF as a primary procedure versus those undergoing a primary prosthetic replacement using the Fisher exact t test assuming equal variances. The primary outcome variable for this analysis was the presence or absence of a major complication and the need for revision surgery. For our subset of patients undergoing primary ORIF, comparison of patients who had nonunions versus those who had union was performed. The same univariate analysis was performed with a designated null hypothesis set for each categorical variable using the Fisher exact t test assuming equal variances. To correct for multiple comparisons, we applied the Bonferroni correction to an alpha error of 0.05, making our p value for significance 0.025. Multivariable analysis was not performed due to the limited number of events in the study. Statistical analysis was performed using the Microsoft® Excel® data analysis function (Microsoft Corp, Redmond, WA).

Results

Patients undergoing ORIF had more ($p = 0.007$) major complications (1.97 versus 0.167) and more ($p = 0.027$) revision surgeries (2.30 versus 1.17) than patients undergoing prosthetic replacement. Nineteen of the 30 (63%) fractures in the ORIF group developed a nonunion. Bone grafting data were available for only 22 of 30 patients. None of the patients for whom information was available had bone graft used at index operation and six patients had bone graft (allograft or vascularized fibula) used at revision surgery. All 19 nonunions underwent revision surgery between 3 and 48 months after index surgery. Nonunions persisted with the need for additional revision surgery in six of the 19 fractures (32%).

Of the six fractures treated with index prosthetic replacement, one had subsequent revision surgery 23 months after index surgery because of loosening of the prosthesis. One patient had a distal femoral replacement and subsequently developed a fracture in the diaphysis that

Table 3. ORIF group analysis of healed versus nonhealed fractures

Characteristic	Healed (n = 11)	Nonhealed (n = 19)	P value
Age (years)*	61.4	68.2	
Gender (male:female)	4:7	8:11	0.767
Fracture location			0.006
Metaphyseal	5	1	
Diaphyseal	6	18	
Fracture pattern			< 0.0001
Displaced	3	18	
Nondisplaced	8	1	
Number of surgeries			0.004
1	8	4	
> 1	3	15	
Tumor size (cm)*	5.6	13.5	
Tumor grade (AJCC grading system)			0.093
High	8	18	
Low	3	1	
Periosteal stripping			0.956
Yes	8	14	
No	3	5	
Interval to healing (months)*	14.2	26.3	0.003
Time after radiation fracture occurred (years)*	3.4	3.5	
Total radiation dose (cGy)*	5932.91	5907.16	
Complications (presence or absence)			0.0001
None	8	2	
1 or more	3	17	

* Values are expressed as means; ORIF = open reduction internal fixation; AJCC = American Joint Committee on Cancer.

required revision surgery with a longer prosthesis. This fracture, which developed above the prosthesis, was also located within the field of radiation. The other five patients underwent prosthetic replacement with a proximal femoral replacement (one), long-stem hemiarthroplasty (one), and distal femoral replacements (two). There were no prosthetic infections among these six patients.

Given the higher rates of complications and reoperations, we examined the subgroup of 30 fractures that underwent index ORIF (healed, $n = 11$; nonhealed, $n = 19$) for characteristics associated with high complications. Metaphyseal fracture location ($p = 0.006$) and nondisplaced fracture patterns (unicortical stress fracture according to our definition above) ($p < 0.0001$) were more likely to heal from index ORIF surgery without the need for revision surgery and have a lower number of complications (Table 3). There were no differences seen based on gender, tumor grade, or periosteal stripping. As expected, those patients who healed with index ORIF without the

need for revision surgery had shorter ($p = 0.003$) interval healing times (14.2 months versus 26.3 months).

Discussion

High-dose radiation affects bone healing, making operative management of radiation-induced fractures difficult. Often prosthetic replacement is the last option for limb salvage. We reviewed our experience with fractures after soft tissue sarcoma resection and radiation therapy and compared patients' treatments with complication rates and rates of revision surgery to see which treatment led to the least patient morbidity.

We recognize limitations to our study. First is the small event number. However, postradiation fractures are not common after soft tissue sarcoma resection and this is the largest single center reported series in the literature. Although we had only six patients who underwent primary prosthetic replacement, our low rate of complications was striking. None of these patients required revision surgery for problems related to nonunion or infection. Similarly, we found lower complication rates among patients with metaphyseal fractures who underwent ORIF. Only one ORIF patient had metaphyseal nonunion (17%) as opposed to 18 of 24 diaphyseal nonunions (75%) and the number of reoperations was less for patients who had primary prosthetic replacement (17%) than for those patients after primary ORIF (63%). A second limitation of the study is the missing data. There were two patients for whom information about the size of the lesion excised and periosteal stripping was not found in the chart and operative reports. Additionally, eight patients in the study had their initial surgery performed at an outside hospital. These patients underwent ORIF at index operation and did not have operative reports available for review to assess bone graft use and intraoperative findings. The main questions of our study did not involve these variables and we believe they would have had minimal effect, if any, on our main conclusions.

The reported prevalence of radiation-associated fractures in heterogeneous populations after treatment for soft tissue sarcoma varies from 5% to 15% [4, 13, 21]. The results may be site specific. For example, a recent study from our institution reported a prevalence of 22% (22 of 101) for fractures in the femur [20]. Radiation-induced fractures are difficult to manage and heal poorly. Because of the high failure rates of conventional treatment of established fractures, alternative methods to manage these fractures have been suggested [12, 13].

The literature highlights similarly high complication rates in postradiation-associated fractures (Table 4). Helmstedter et al. [10] reported a nonunion rate of 45% and

Table 4. Nonunion rates seen in our study and in other studies

Study	Nonunion rate	Total number of patients in the study	Overall complication rate (all types)
Donati et al. [5]	57%	113	75%
Helmstedter et al. [10]	45%	20	65%
Lin et al. [13]	75%	12	75%
Kim et al. [current study]	63%	39	58%

deep infection rate of 20%. They concluded prophylactic nailing should be considered in patients undergoing resection of large anterior compartment tumors of the thigh where there is extensive periosteal stripping and adjuvant radiation therapy. A larger series by the European Musculoskeletal Oncology Society reported a complication rate of 75%, which included infections and nonunions [5]. Moreover, the complications in that series had lasting consequences. Among those patients who had surgery for complications, only 63% had good results. All revision surgeries used allografts and none used endoprosthetic replacements. Clearly, this subset of patients suffers high morbidity from their fractures, needing multiple hospitalizations and revision surgeries.

One of our aims was to determine which factors might minimize this morbidity, as well as to explore what patient risk factors might inform the decision-making process. Among patients with diaphyseal fractures, 18 of 24 (75%) had a major complication and required revision surgery with either a vascularized fibula graft or allograft. This rate of nonunion is similar to that in the literature but is nonetheless high (Table 4). Our relatively low complication rate of 17% in those patients who underwent primary endoprosthetic replacement for fractures suggests a subset of patients may benefit from this method of treatment over primary ORIF.

Proponents for ORIF at index surgery may criticize endoprosthetic replacement as an excessively radical first-line surgical treatment option. Despite the legitimate question about sacrificing an adjacent joint and sustaining the risk of a catastrophic prosthetic infection in radiated soft tissue with disrupted vasculature, these concerns are not limited to prosthetic replacement. For example, joint function is seriously compromised by repeat surgeries and prolonged restriction of activity during bone healing after ORIF. Nonunion rates associated with these patients are greater than 45% in the literature and, in our experience, even higher at 63% [9–13]. These nonunions required revision surgery and, in a number of cases, more than two revision surgeries, which further compromised the soft tissues. Additionally, there has yet to be a report in the literature of prosthetic infection rates substantially greater than those seen with ORIF in this subset of patients [16]. In

this small cohort, the high rates of persistent nonunion, reoperation, and infection make ORIF the more dangerous procedure.

Primary prevention strategies, such as prophylactic nailing, may be attractive options but should be reserved for patients with an inordinately high fracture risk. Previous studies have suggested female gender [13], periosteal stripping [10, 13], anterior and medial lesions [10, 20], circumferential resections [13], and high-dose radiation (> 60 Gy) [11] as factors predisposing patients to fractures. Recently, Gortzak et al. [8] formulated a scoring system based on multiple regression analysis of clinical risk factors in their study group patients. Using a model they reported to be 91% sensitive and 81% specific for predicting radiation-associated fracture risk, they concluded patient age, gender, and tumor size were the most important risk factors. Further studies to validate this model will be an essential addition to the clinical treatment of radiation-induced fractures after soft tissue sarcoma resection.

Although tumor location is a risk factor for fracture, no study has determined whether location influences the probability of fracture healing. The high failure rate of primary ORIF deserves more scrutiny.

Using a vascularized fibular graft has been suggested as a method to augment the fracture fixation and aid healing [10, 13]. However, in our series, four patients received a vascularized fibular graft at their third or fourth surgical attempt at fixation and, of these, only two went on to heal. There were also two major wound-healing problems and infections. Thus, vascularized fibular grafts were not dependable in our series. The results failed to match the theoretic appeal of a biologic solution for fractures in a severely compromised tissue envelope.

Larger studies are needed to validate any treatment algorithm for patients developing radiation-induced fractures after soft tissue sarcoma resection. Based on our findings, we believe prosthetic replacement rather than ORIF will allow for early mobilization and less need for revision surgery for patients with postradiation femur fractures.

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