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Radiation-Associated Femoral Nonunion and Fixation Failure Following Limb-Salvage Surgery for Thigh Soft-tissue Sarcoma: Two Case Reports and a Review of the Literature

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Learning Point of the Article:

Persistent unexplained thigh pain in previously irradiated femurs following limb-salvage surgery may indicate impending biomechanical failure requiring early reconstructive intervention.

Abstract

Introduction: Femoral fractures following combined surgery and radiotherapy for soft-tissue sarcomas of the anterior thigh are uncommon but clinically challenging complications. Reported outcomes vary widely, with internal fixation frequently complicated by delayed union, non-union, or mechanical failure, particularly in the setting of irradiated bone and additional patient- or treatment-related risk factors.

Case Report: In this report, we describe two patients with high-grade anterior thigh soft-tissue sarcomas treated with limb-sparing surgery and radiotherapy who subsequently developed femoral fractures within the irradiated field. Both patients underwent intramedullary nail fixation and progressed to non-union with fixation failure, necessitating salvage with distal femur endoprosthetic reconstruction. One patient achieved durable limb salvage following reconstruction, whereas the second developed progressive soft-tissue compromise and periprosthetic infection, ultimately requiring above-knee amputation.

Conclusion: These cases highlight the complexity of managing femoral fractures in irradiated bone and underscore the limitations of fixation strategies reliant on biologic healing in high-risk patients. Persistent, unexplained thigh pain may represent an early warning sign of impending mechanical failure. Early risk stratification and timely consideration of reconstructive strategies that provide immediate mechanical stability may help mitigate morbidity in select patients following limb-salvage treatment for soft-tissue sarcoma.

Keywords: Soft-tissue sarcoma, radiation-associated femoral fracture, nonunion, distal femur replacement, limb salvage.

Introduction

Limb-salvage surgery combined with radiotherapy is the standard of care for high-grade soft-tissue sarcomas of the extremities. Although this approach provides excellent local tumor control, radiation-induced injury to bone and surrounding soft tissues may predispose patients to insufficiency fractures, delayed union, non-union, and fixation failure [1,2,3]. Management of femoral fractures in this setting is particularly challenging due to compromised bone biology, altered biomechanics, and diminished healing capacity resulting from prior oncologic treatment. We present two cases of radiation-associated femoral nonunion following limb-salvage treatment for thigh sarcoma, illustrating divergent clinical courses, and reconstructive outcomes.

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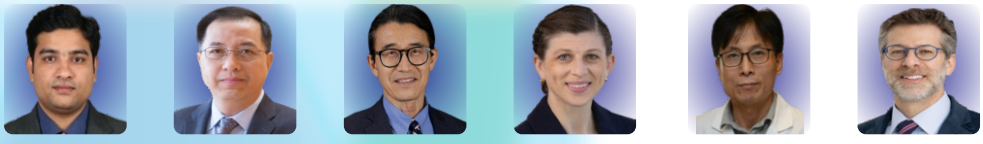

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Case Report

Case 1

A 58-year-old male with a history of Type 2 diabetes mellitus, hypertension, hyperlipidemia, gout, and morbid obesity (body mass index [BMI] 46.20 kg/m2) who presented with several months of progressive atraumatic right thigh pain and swelling. Magnetic resonance imaging demonstrated a large heterogeneous intramuscular mass involving the anterior compartment of the thigh concerning a high-grade soft-tissue sarcoma. Open biopsy confirmed a dedifferentiated liposarcoma characterized by high-grade pleomorphic spindle cells with MDM2 amplification. Following multidisciplinary tumor board discussion, neoadjuvant radiotherapy followed by wide local excision was recommended.

The patient completed neoadjuvant external beam radiotherapy to a total dose of 50 Gy delivered in 25 fractions and subsequently underwent wide local resection through an anteromedial approach with en bloc resection of the involved anterior compartment musculature. Limited anterior and medial periosteal stripping of the femur was required to achieve oncologic clearance, without posterior or lateral cortical disruption. Primary closure was achieved without flap reconstruction. Final pathology demonstrated a high-grade dedifferentiated liposarcoma with marked treatment effects and R0 margins.

Five months postoperatively, surveillance imaging revealed bilateral pulmonary metastases, prompting initiation of systemic chemotherapy with the AIM regimen (doxorubicin, ifosfamide, and mesna), followed by staged pulmonary metastasectomies.

Postoperatively, the patient achieved full post-operative recovery with full weight bearing, full knee range of motion, and independent ambulation using a cane, which was a return to his baseline function. Eight months following surgical resection, he developed progressive distal thigh pain. Interval magnetic resonance imaging demonstrated a large post-operative seroma and a subcutaneous, 2 cm soft-tissue lesion in the anterior distal thigh. The lesion was localized to the subcutaneous tissues, was tender to palpation, and demonstrated no overlying skin changes, erythema, or warmth. Given its focal nature and superficial location, it was initially considered a possible contributor to the patient's localized pain. However, in the absence of radiographic features suggestive of impending fracture or osseous compromise, and with preservation of full weight bearing, knee range of motion, and overall functional status, prophylactic fixation was deferred.

Ten months after index surgery, the patient sustained a low-energy trauma while ambulating, resulting in a distal femoral shaft fracture. Preoperative imaging and intraoperative biopsy from the fracture site demonstrated no evidence of recurrent or metastatic sarcoma. The fracture was treated surgically with retrograde intramedullary nailing. At 12 months from index surgery, following systemic therapy, the patient underwent staged bilateral pulmonary metastasectomies, achieving complete resection of metastatic disease.

Despite excellent reduction, substantial bony apposition, and stable fixation, the patient presented 15 months follow-up with acute pain and an inability to bear weight. Imaging confirmed implant failure through one of the distal interlocking screws, confirming non-union at the fracture site. He was indicated for removal of hardware and reconstruction using a right distal femur replacing a rotating hinge endoprosthesis as definitive management. Surgical goals included durable limb salvage, independent of fracture healing, and immediate post-operative weight bearing. The symptomatic anterior distal thigh soft-tissue lesion was excised concurrently, with final pathology demonstrating a well-circumscribed benign epithelial neoplasm consistent with spiradenoma, a painful sweat gland tumor, explaining the patient's localized anterior thigh pain and confirming the absence of malignant disease.

Case 2

A 52-year-old male with a medical history significant for morbid obesity (BMI 43.53 kg/m2), hypertension, obstructive sleep apnea, and metastatic alveolar soft part sarcoma of the anterior thigh presented with progressive lower-extremity pain and functional decline. His oncologic history dated back more than two decades, when he underwent wide resection of anterior thigh sarcoma followed by combined brachytherapy, external beam radiation therapy, and multiagent chemotherapy (doxorubicin, ifosfamide, dacarbazine). Pulmonary nodules developed 2 years after his initial diagnosis, and he was managed with resection, inhalation doxorubicin on a clinical trial, liposomal doxorubicin, and capecitabine. Eight years from diagnosis, he initiated sunitinib, and his disease remained clinically quiescent with ongoing oncologic surveillance.

Approximately 1 year before presentation (20 years after initial sarcoma excision), he sustained a low-energy traumatic event resulting in a closed, extra-articular distal femoral fracture within the previously irradiated field. He underwent intramedullary nail fixation at an outside institution but experienced persistent pain and progressive functional limitation. Subsequent evaluation demonstrated femoral nonunion with implant failure, including fracture of the nail and a distal interlocking screw.

Given the history of prior radiation exposure and failed fixation,

he underwent removal of hardware with an open biopsy followed by distal femur endoprosthetic reconstruction. His pathology was negative for recurrence of sarcoma or infection. Although early post-operative recovery was initially satisfactory, his course was complicated by progressive ipsilateral lower-extremity lymphedema, increasing pain, swelling, and eventually malodorous wound drainage consistent with deep infection. The initial debridement surgery revealed significant necrotic, poorly vascularized soft tissues in the previously radiated field and extensive purulence throughout the thigh and leg compartments. His periprosthetic joint infection was due to klebsiella pneumoniae and enterococcus faecalis. Due to polymicrobial infection, compromised soft-tissue envelope, and poor healing potential, he elected to proceed with an above-knee amputation. His immediate post-operative course was smooth; he was discharged to an inpatient rehabilitation facility for post-operative recovery and functional rehabilitation for 2 weeks and then transitioned home. He completed an oral regimen of Augmentin for 2 weeks as an outpatient. Gabapentin was initiated for phantom limb discomfort, and he weaned from narcotics within 3 weeks.

Discussion

Femoral fractures following limb-salvage surgery combined with radiotherapy for soft-tissue sarcoma are uncommon but clinically consequential. Reported fracture incidence ranges from 2% to 22%. This may be impacted by heterogeneity in radiation dose, treatment technique, extent of surgical exposure, and patient-specific risk factors [1,2,3,4]. Femoral fracture risk has been reported to be related to several variables, including anatomic location, limb-sparing surgery, length of resection, and degree or extent of periosteal disruption [1,4,5,6]. Larger contemporary series further confirmed that femoral fracture remains an important late complication despite advances in multidisciplinary sarcoma care [2,3,5,7]. Previously published reports relevant to fracture risk, radiation-associated bone injury, fixation failure, and reconstructive outcomes are summarized in Table 1.

Radiation-associated skeletal injury is mediated through several well-described biological mechanisms. Ionizing radiation suppresses osteoblast proliferation and differentiation, increases osteoclast-mediated resorption, and damages the microvascular supply required for cortical bone viability and fracture healing [8,9,10]. These biological effects culminate in reduced bone mineral density, impaired remodeling, and diminished reparative capacity. Experimental work by Willey et al. demonstrated an early increase in osteoclast activity after radiation exposure, providing a mechanistic basis for the progressive bone fragility seen clinically in irradiated femora [9]. Clinically, insufficiency fractures may occur months to years after treatment, underscoring the durable nature of radiation-induced skeletal toxicity [8,11].

Radiation dose and dose distribution also influence fracture risk. Prior work has shown that fracture risk increases with higher cumulative radiation exposure, particularly when the anterior femoral cortex is included within the high-dose field [2,3,5,12,13,14]. Because the anterior cortex is subjected to greater tensile stress during ambulation, this region may be particularly vulnerable after radiation-induced weakening. Although modern radiotherapy techniques such as intensity-modulated radiotherapy (IMRT) have improved dose conformality and reduced exposure to uninvolved bone, femoral fractures continue to occur, suggesting that surgical factors and host-related variables remain important contributors to skeletal toxicity [3,12,14].

Surgical technique remains another critical determinant of fracture risk. Preservation of the periosteum and maintenance of cortical vascularity are important for cortical viability after radiation exposure. Multiple series have demonstrated that extensive periosteal stripping during tumor resection substantially increases the likelihood of subsequent femoral fracture [1,5,6,10]. At the same time, more recent literature suggests that periosteal injury should not be viewed in isolation. Pak et al., showed that femoral fractures can occur even without extensive periosteal stripping, emphasizing that fracture risk is multifactorial and likely reflects the combined effects of radiation injury, altered biomechanics, surgical exposure, and host characteristics [7]. Predictive modeling studies have similarly suggested that cumulative risk is better explained by the interaction of several moderate-risk variables rather than any single feature alone [15].

Patient-related characteristics further influence both fracture risk and reconstructive outcomes. Morbid obesity, present in both currently reported cases, increases mechanical loading across the femur and may magnify cantilever stresses in already compromised bone [16,17]. In addition, radiation fibrosis and loss of functional musculature may alter force transmission and reduce dynamic stabilization of the femur. Obesity is associated with increased wound complications, infection, and implant failure following limb-salvage surgery and megaprosthetic reconstruction, underscoring additional risks with which it is associated [16,17].

A clinically important observation in both of the currently presented cases was the presence of persistent unexplained thigh pain preceding either fracture or fixation failure. Pain has been recognized as an early clinical indicator of impending structural compromise in oncologic bone disease, even when

Table 1: Literature review of reported femoral fractures following limb-salvage surgery and radiotherapy for extremity soft-tissue sarcoma

Author	Year	Journal	Study type	Key findings
Damron and Sim	1993	Clin Orthop Relat Res	Observational	Pain may precede pathologic fracture and signal impending structural failure
Lin *et al* .	1998	J Bone Joint Surg Am	Retrospective	High rates of delayed union and fixation failure in irradiated femur
Holt *et al* .	2005	J Bone Joint Surg Am	Cohort	Periosteal stripping significantly increased fracture risk
Gortzak *et al* .	2005	Ann Surg Oncol	Risk model	Developed predictive model for radiation-associated femoral fracture
Davis *et al* .	2005	Clin Orthop Relat Res	Case series	Internal fixation frequently fails in irradiated bone
Coleman	2006	Clin Cancer Res	Review	Bone pain associated with impending skeletal morbidity
Jeys *et al* .	2007	J Bone Joint Surg Br	Cohort	Obesity associated with increased wound complications
Myers *et al* .	2007	J Bone Joint Surg Br	Case series	Distal femoral endoprosthetic replacement effective for reconstruction
Willey *et al* .	2008	Radiat Res	Experimental	Radiation increases osteoclast activity and bone resorption
Sugimoto *et al* .	2009	Skeletal Radiol	Case series	Radiation insufficiency fractures may occur years after treatment
Henderson *et al* .	2011	Clin Orthop Relat Res	Classification study	Defined failure modes of tumor endoprostheses
Bedi *et al* .	2012	J Bone Joint Surg Am	Cohort	Radiation dose and surgical exposure increase fracture risk
Pak *et al* .	2012	Clin Orthop Relat Res	Multicenter	Femoral fractures reported even without extensive periosteal stripping
Biau *et al* .	2012	Eur J Surg Oncol	Cohort	Limb salvage effective, but late complications persist
Dickie *et al* .	2013	Bone Joint J	Cohort	Fracture incidence ~7% following limb preservation surgery
Bishop *et al* .	2013	Cancer Control	Review	Overview of combined surgery and radiotherapy in extremity STS
Baldini *et al* .	2013	Ann Surg Oncol	Cohort	Identified predictors for major post-operative complications
Folkert *et al.*	2014	Int J Radiat Oncol Biol Phys	Cohort	IMRT reduces but does not eliminate femoral fracture risk
Cannon *et al* .	2014	Int J Radiat Oncol Biol Phys	Cohort	High radiation dose to anterior femur associated with fractures
Perry *et al* .	2014	Clin Orthop Relat Res	Cohort	BMI increases risk of infection and implant failure
Bishop *et al* .	2016	J Clin Oncol	Cohort	Persistent fracture risk after definitive radiotherapy
Pala *et al* .	2016	Bone Joint J	Cohort	Megaprosthetic reconstruction effective for femoral defects
Errani *et al* .	2017	Bone Joint J	Cohort	Durable limb salvage with megaprosthetic reconstruction
Beane *et al* .	2018	Sarcoma	Review	Long-term skeletal toxicity after sarcoma therapy

imaging findings are subtle [18,19]. In the setting of a previously irradiated femur, persistent focal pain should therefore prompt heightened suspicion for evolving biomechanical failure and may justify closer surveillance, additional imaging, or earlier intervention.

Management of femoral fractures in irradiated bone remains particularly challenging because internal fixation relies on biologic healing in a host environment where fracture repair is impaired [4,8,20]. Earlier reports of fixation in irradiated femora documented substantial rates of delayed union, non-union, and mechanical failure [4,20]. These limitations help explain why intramedullary fixation may be insufficient in selected high-risk patients, even when alignment and implant position are satisfactory at the index fracture surgery.

For this reason, several authors have advocated consideration of endoprosthetic reconstruction in select patients with radiation-associated femoral fracture or failed fixation [21,22,23,24]. Endoprosthetic reconstruction provides immediate mechanical stability, allows early weight bearing, and eliminates dependence on fracture healing [22,23,24]. Long-term studies of distal femoral and megaprosthetic reconstruction have demonstrated that this approach can provide durable limb salvage, although outcomes remain heavily dependent on host biology, soft-tissue envelope quality, and infection risk [17,21,22,23,24].

The present report adds to the literature in several important ways. First, it describes two distinct clinical trajectories after radiation-associated femoral fractures in patients treated for thigh soft-tissue sarcoma; one successfully salvaged with distal femoral endoprosthetic reconstruction and another progressing to infection and eventual amputation. Second, these cases highlight persistent unexplained thigh pain as a potential early warning sign of impending mechanical compromise in irradiated bone. Finally, the cases emphasize the limitations of fixation strategies that rely on biologic fracture healing in previously irradiated bone and support consideration of reconstructive options that provide immediate mechanical stability in appropriately selected high-risk patients.

Taken together, these cases illustrate a spectrum of outcomes associated with radiation-related femoral fracture after limb-salvage treatment for soft-tissue sarcoma. These divergent outcomes underscore the need for careful risk stratification, vigilance for early clinical warning signs, and individualized decision-making when treating femoral fractures in irradiated bone.

Conclusion

These two cases illustrate the spectrum of radiation-associated femoral fractures following limb-salvage treatment for high-grade soft-tissue sarcoma. Case 1 demonstrates successful salvage with distal femur replacement following fixation failure, whereas Case 2 underscores the potential for catastrophic complications, including infection and limb loss, despite aggressive reconstructive efforts. Persistent unexplained thigh pain should prompt heightened suspicion for biomechanical compromise in irradiated extremities. Early risk stratification and timely consideration of reconstructive strategies that minimize reliance on biologic healing may help reduce morbidity in select high-risk patients.

Clinical Message

Persistent, unexplained thigh pain in a previously irradiated extremity following limb-sparing sarcoma resection should raise concern for underlying biomechanical compromise, even when imaging does not demonstrate an overt fracture. In high-risk patients – particularly those with substantial radiation exposure, morbid obesity, or significant post-radiation fibrosis – early consideration of prophylactic stabilization or definitive reconstruction may help prevent fracture and avert the cascade of complications associated with fixation failure, infection, and limb loss.

Declaration of patient consent: The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given the consent for his/ her images and other clinical information to be reported in the journal. The patient understands that his/ her names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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