American Journal of Case Reports

e-ISSN 1941-5923
© Am J Case Rep, 2022; 23: e934372
DOI: 10.12659/AJCR.934372

Received: 2021.08.11
Accepted: 2021.10.27
Available online: 2021.11.29
Published: 2022.01.15

Successful Management of Radiation-Associated Insufficiency Fracture of the Tibial Plateau with Low-Intensity Pulsed Ultrasound

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABDE 1 **Tomoya Matsunobu**
BD 1 **Akira Maekawa**
BD 2 **Satoshi Nomoto**
DE 1 **Yukihide Iwamoto**

1 Department of Orthopedic Surgery, Kyushu Rosai Hospital, Kitakyushu, Fukuoka, Japan
2 Department of Radiology, Kyushu Rosai Hospital, Kitakyushu, Fukuoka, Japan

Corresponding Author: Tomoya Matsunobu, e-mail: matsunob.orth-k@kyushuh.johas.go.jp
Financial support: This work was supported in part by the Practical Research for Innovative Cancer Control from the Japan Agency for Medical Research and Development, AMED (20ck0106614h0001)
Conflict of interest: None declared

Patient: Female, 52-year-old
Final Diagnosis: Fracture
Symptoms: Knee pain
Medication: —
Clinical Procedure: —
Specialty: Oncology

Objective: Unusual or unexpected effect of treatment

Background: Clinical management of radiation-associated pathological fracture is challenging because of a high nonunion rate and potential for morbidity. We report a case of radiation-associated insufficiency fracture of the tibial plateau after surgery, perioperative chemotherapy, and adjuvant radiation therapy for synovial sarcoma of the proximal calf that was successfully treated with low-intensity pulsed ultrasound (LIPUS).

Case Report: A healthy 52-year-old Japanese woman presented with a slowly growing, painful soft tissue mass over her proximal calf. Histological examination of core needle biopsy specimens led to a pathological diagnosis of synovial sarcoma. After perioperative ifosfamide and doxorubicin chemotherapy and surgical resection, adjuvant radiation therapy was administered, with a total of 60 Gy in 30 fractions. At 5 months after surgery and 2 months after the completion of radiation therapy, she developed an insufficiency pathological fracture of the proximal tibia without any apparent trauma. The patient was treated with LIPUS for 1 year. There was no collapse or deformity of the knee joint. The patient remained free of symptoms and had no recurrences for 2 years after surgery.

Conclusions: This is the first report of radiation-associated pathological fracture that was successfully treated with LIPUS. LIPUS could be a safe and effective treatment option in the management of radiation-associated pathological fractures.

Keywords: Fractures, Bone • Radiotherapy • Sarcoma • Ultrasonic Waves

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/934372

Indexed in: [PMC] [PubMed] [Emerging Sources Citation Index (ESCI)] [Web of Science by Clarivate]

Background

Wide local resection is the mainstay of treatment for high-grade soft tissue sarcoma in the extremities [1]. The addition of (neo)adjuvant radiation therapy (RT) improves local control after surgical resection [2]. Since soft tissue sarcoma has moderate radiation sensitivity, the recommended postoperative radiation dose is 60-66 Gy in 1.8-2 Gy fractions [3]. RT is associated with various complications including skeletal complications, skin disorders, joint stiffness, joint fibrosis, joint contracture, pain, lymphedema, and neuropathy [2]. Depending on the tumor location, concomitant surgical resection of the periosteum might be required; periosteum stripping and RT reportedly increase the risk of the pathological fracture [4]. Treatment of post-radiation fractures can be challenging. Several studies have reported a nonunion rate as high as 45% in patients with sarcoma who have post-radiation fractures [5].

Recently, low-intensity pulsed ultrasound (LIPUS) has been widely used to treat fresh and nonunion fractures [6]. We report a case of radiation-associated insufficiency fracture of the tibial plateau after surgery and RT for synovial sarcoma of the calf that was successfully treated with LIPUS.

Case Report

A 52-year-old Japanese woman with no significant medical history presented with a slowly growing and painful mass over her proximal calf. Her height and weight were 146.9 cm and 57.2 kg, respectively. Her body mass index was 27.67 kg/m^2. Her physical examination revealed a hard, tender, palpable 6×5 cm mass with moderate mobility under the right proximal calf without restriction of right knee range of motion. On laboratory testing, serum calcium and phosphorus and renal and liver function were within normal limits. Plain radiographs of the right knee showed no abnormalities caused by the soft tissue tumor or osteoarthritis (**Figure 1**). The lesion, measuring 72×22×17 mm on magnetic resonance imaging (MRI), appeared as a tumor with clear margins in the popliteus muscle. The lesion had low and high signal intensity on T1- and T2-weighted images, respectively (**Figure 2**). Mild internal enhancement was observed on gadolinium-enhanced fat-suppressed T1-weighted images (**Figure 2**). Chest computed tomography (CT) revealed no apparent lung metastasis (data not shown). CT-guided core needle biopsy was performed. Histopathology findings were consistent with synovial sarcoma, monophasic type (**Figure 3**). Polymerase chain reaction showed *SS18-SSX1*

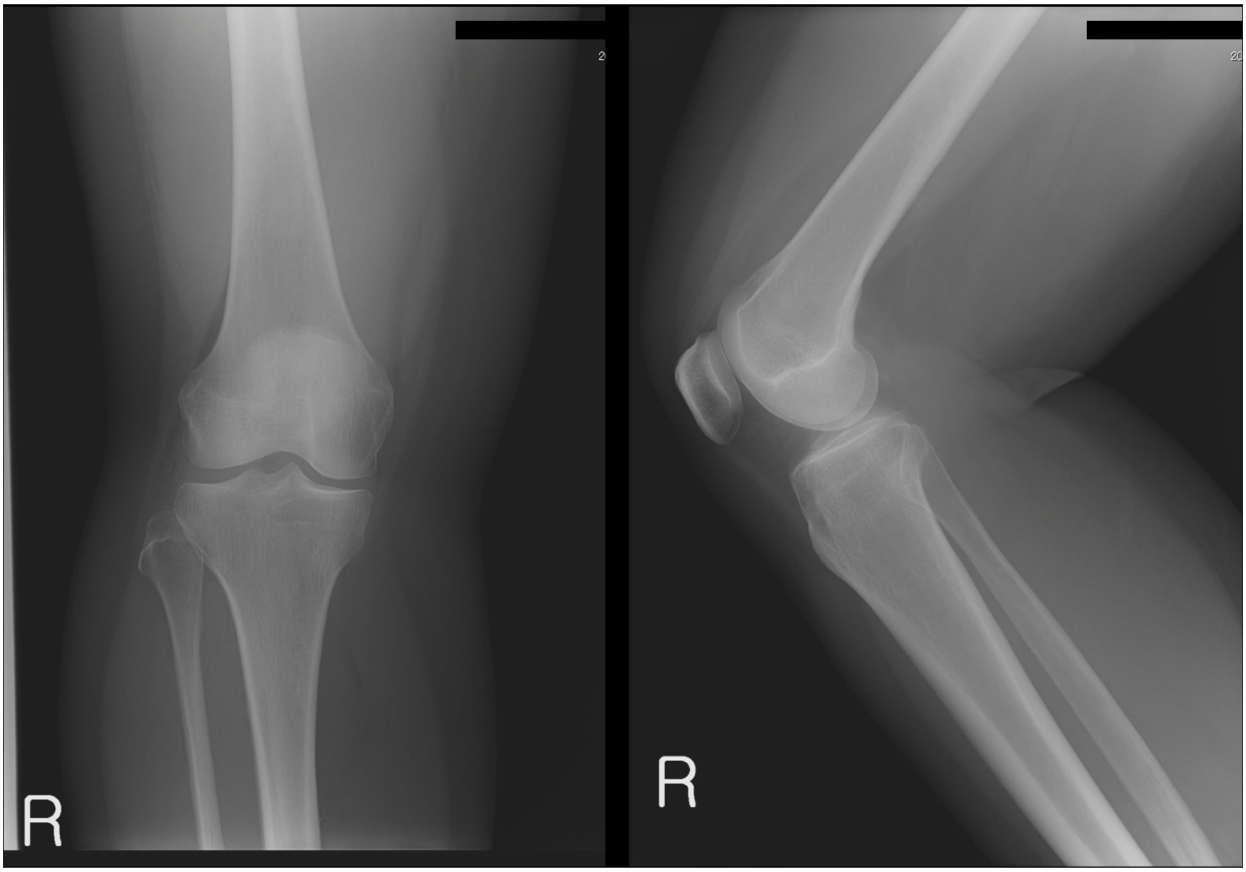


Figure 1. Plain radiographs of the knee joint at the first visit showed no abnormalities caused by the soft tissue tumor or osteoarthritis.

Indexed in: [PMC] [PubMed] [Emerging Sources Citation Index (ESCI)] [Web of Science by Clarivate]

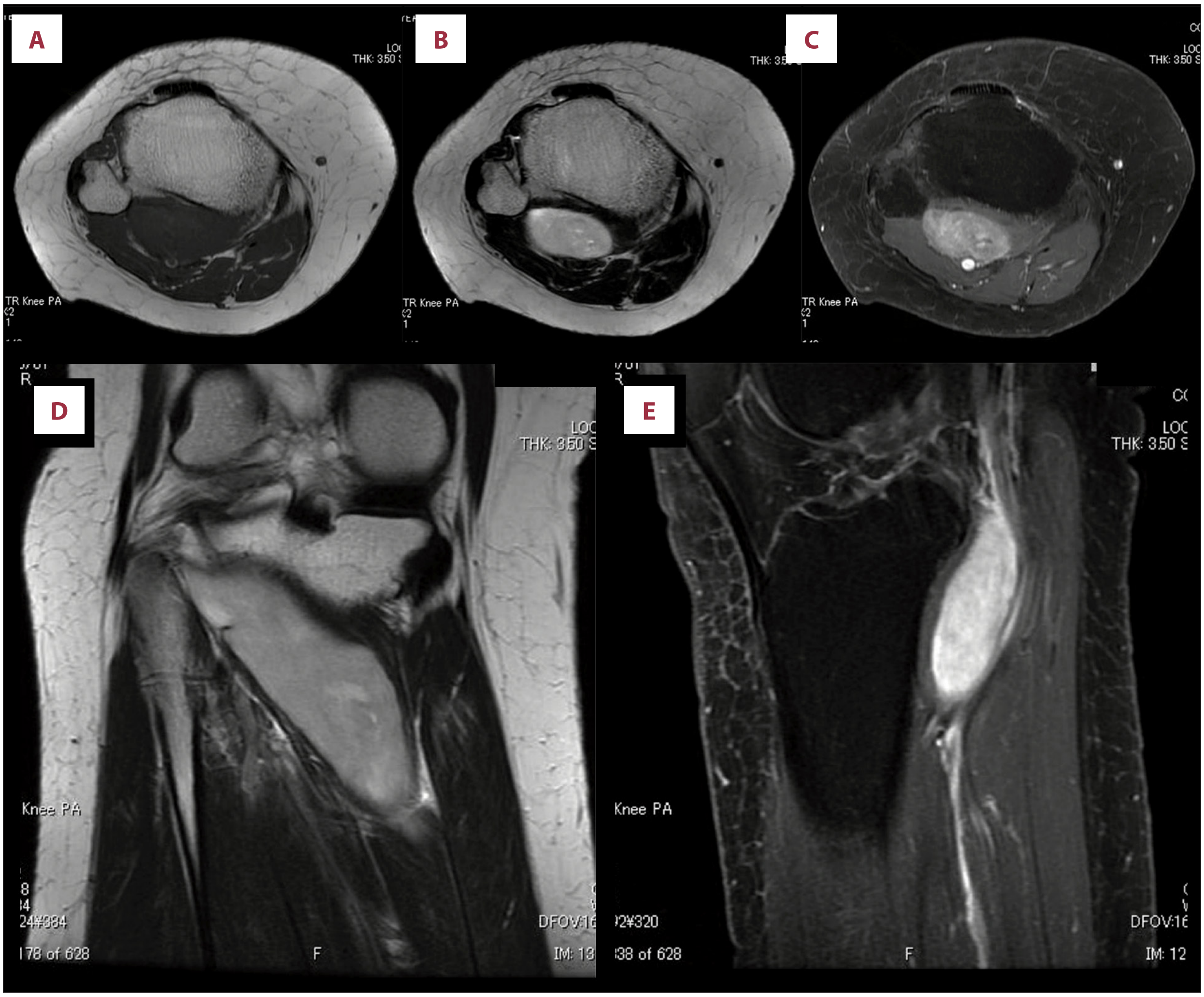


Figure 2. Magnetic resonance imaging (MRI) showed a tumor with clear margins in the popliteus muscle. (**A, B**) T1- and T2-weighted axial images, respectively. (**C**) Gadolinium-enhanced fat-suppressed T1-weighted axial image. (**D**) T2-weighted coronal image. (**E**) T2-weighted sagittal image with fat suppression.

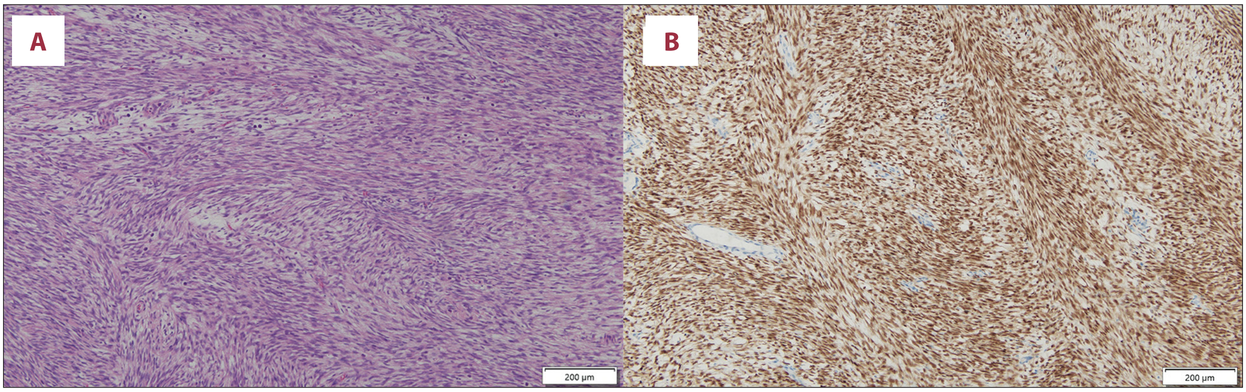
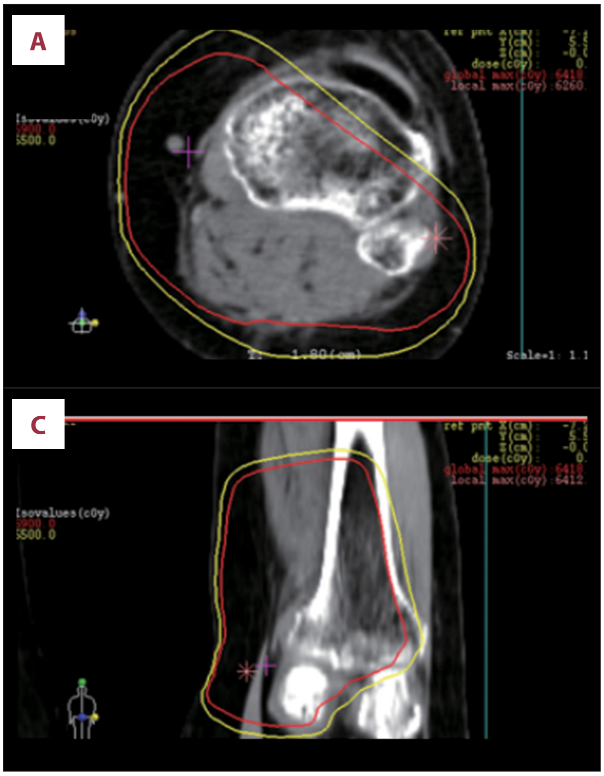


Figure 3. (**A**) Microscopic image of the biopsy specimen (hematoxylin-eosin; HE) showed a densely cellular monomorphic population of spindle cells with focally whorled areas. (**B**) Immunohistochemical staining with an anti-SS18-SSX fusion-specific antibody revealed strong diffuse nuclear positivity.

Indexed in: [PMC] [PubMed] [Emerging Sources Citation Index (ESCI)] [Web of Science by Clarivate]



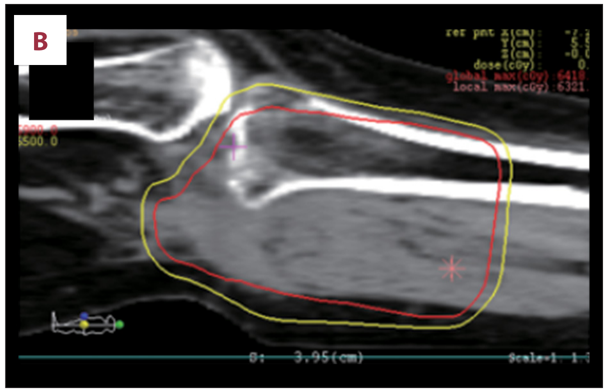


Figure 4. Dose distribution of the radiation therapy was shown. Note the dose of 59 Gy was delivered to the posterior segment of the tibia (red line). (**A**) Axial view, (**B**) sagittal view, and (**C**) coronal view.

gene rearrangement (data not shown). After 3 courses of neoadjuvant chemotherapy with ifosfamide and doxorubicin hydrochloride, we performed surgery.

Preoperative imaging showed no apparent bone invasion. Therefore, the entire popliteus muscle and the adjacent tibial periosteum were resected. Although we assumed that a negative-margin R0 resection was achieved, the lesion was in close proximity to the tibial artery and nerve. The postoperative clinical course was uneventful.

After 2 courses of adjuvant chemotherapy with ifosfamide and doxorubicin hydrochloride, adjuvant RT was administered, with a total of 60 Gy in 30 fractions (**Figure 4**). Approximately 5 months after surgery and 2 months after completion of RT, she revisited our outpatient clinic reporting moderate pain in the right knee without any apparent trauma. Plain radiographs showed no obvious abnormal findings (**Figure 5A, 5B, 5G, 5H**). However, MRI revealed transverse bone marrow edema with low signal intensity on T1-weighted images and high signal intensity on T2-weighted images in the proximal medial tibia, indicating an insufficiency pathological fracture caused by RT (**Figure 6**). We assumed that this insufficiency fracture resulted from the stripping of the periosteum from the proximal tibia and adjuvant RT. We also assumed that this would be a refractory fracture. For conventional tibial plateau fractures, internal fixation with locking plates using the minimally invasive percutaneous osteosynthesis technique could be an option. However, we were concerned about postoperative complications such as deep infection because the surrounding soft tissue would be also compromised from RT. Therefore, we decided to use a conservative non-surgical treatment.

The patient was treated with LIPUS generated by a sonic accelerated fracture healing system (SAFHS Exogen, Teijin, Tokyo, Japan) 20 minutes daily for 1 year. In addition to LIPUS, she started non-weight-bearing walking for the first 3 weeks. She was allowed to gradually increase partial weight-bearing as long as she remained pain-free for next 7 months. In particular, initially she only performed partial weight bearing starting at 30% of her body weight for 3 months, and steadily built up to full weight bearing as tolerated for the next 4 months. In total, she was able to walk without crutches at 8 months after initiation of LIPUS therapy. Local tenderness resolved within 6 months. Radiographs taken 3 and 6 months after LIPUS demonstrated intramedullary callus around the transverse fracture line in the proximal medial tibia (**Figure 5C, 5D, 5I, 5J**). Restoration of the trabecular structure was eventually observed without obvious collapse of the articular surface (**Figure 5E, 5F, 5K, 5L**). Knee pain had completely disappeared 1 year after initiation of LIPUS therapy. MRI showed that the low-intensity area on T1-weighted images (**Figure 6A, 6E**, arrows) and the high-intensity area on short TI inversion recovery (STIR) images (**Figure 6I**, arrowhead) both decreased in size over time. No tumor local recurrence or distant metastases were found during 24 months of follow-up. The timeline of the clinical course is summarized in **Figure 7**.

Discussion

Many lines of evidence suggest that adjuvant RT reduces local recurrence rate in the setting of limb-sparing surgery. Many guidelines recommend adjuvant RT if margin-positive

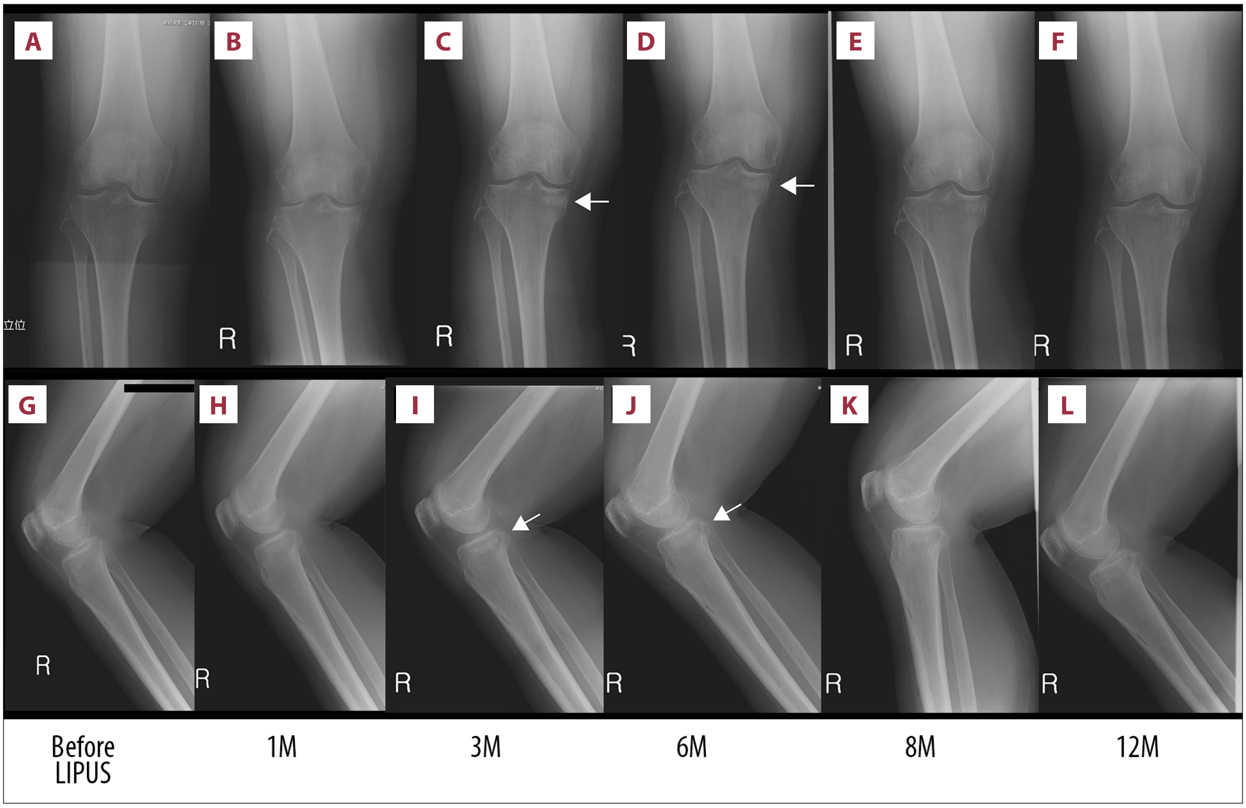


Figure 5. Anteroposterior (**A-F**) and lateral (**G-L**) radiographs of the right knee taken immediately after the onset of the knee pain, and 1 month, 3 months, 6 months, 8 months, and 1 year after initiation of LIPUS therapy. Obvious callus formation around the fracture site was observed at 3 and 6 months after treatment (arrows). After 1 year, remodeling of the fracture callus was complete. LIPUS, low-intensity pulsed ultrasound; M, months.

resection is anticipated [1]. Recent progress in RT has led to better outcomes and fewer adverse events. Although skeletal complications are infrequent, radiation-associated bone fractures are still serious complications in 2-20% of patients treated with limb-sparing surgery and RT [7]. Radiation-associated pathologic fractures tend to have a high nonunion rate and could be a major cause of morbidity. While prophylactic intramedullary nailing is a common approach for preventing radiation-associated fractures, especially in the diaphysis of long bones [4], it has been suggested that prophylactic nailing should not be routinely performed because the risk of fracture is low. Theoretically, minimally invasive techniques such as stabilization with locking plate augmentation could be applicable to any type of tibial plateau fracture. However, there have been no reports that such methods could prevent the collapse of the articular surface in the case of a radiation-associated fracture. In addition, we must be careful because deep infection rates up to 20% after surgery have been reported for radiation-associated fractures in some series [5,8]. Therefore, a simple and easy method to accelerate radiation-associated fracture healing must be developed.

Adverse effects of ionizing radiation are histologically consistent with decreased osteocyte counts, suppressed osteoblastic activity, and diminished vascularity [9,10], which lead to impairment of bone regeneration at a fracture site. LIPUS accelerated the repair of fractures during various steps of the fracture repair process in an animal model [11]. The United States Food and Drug Administration approved LIPUS for fracture healing in 1994 [6]. LIPUS is a clinically established treatment used to accelerate long bone fracture healing. In experimental models, LIPUS played an important role in promoting fracture healing in pathological conditions. Cheung et al reported that in ovariectomized rats, LIPUS was associated with significantly enhanced callus formation, faster mineralization, and better remodeling in the closed femoral fracture group than in the control group [12]. Regarding the effect of radiation on osteogenesis, an in vitro experiment showed that LIPUS restored the viability of suppressed cells and osteogenic differentiation of radiation-damaged rat mandible-derived bone marrow mesenchymal stem cells [13]. In terms of safety, Busse et al reported no adverse events associated with LIPUS treatment in a randomized clinical trial (Re-evaluation of low-intensity pulsed ultrasound in treatment of tibial fractures (TRUST)) [14]. Therefore, LIPUS could be a safe and effective

Indexed in: [PMC] [PubMed] [Emerging Sources Citation Index (ESCI)] [Web of Science by Clarivate]

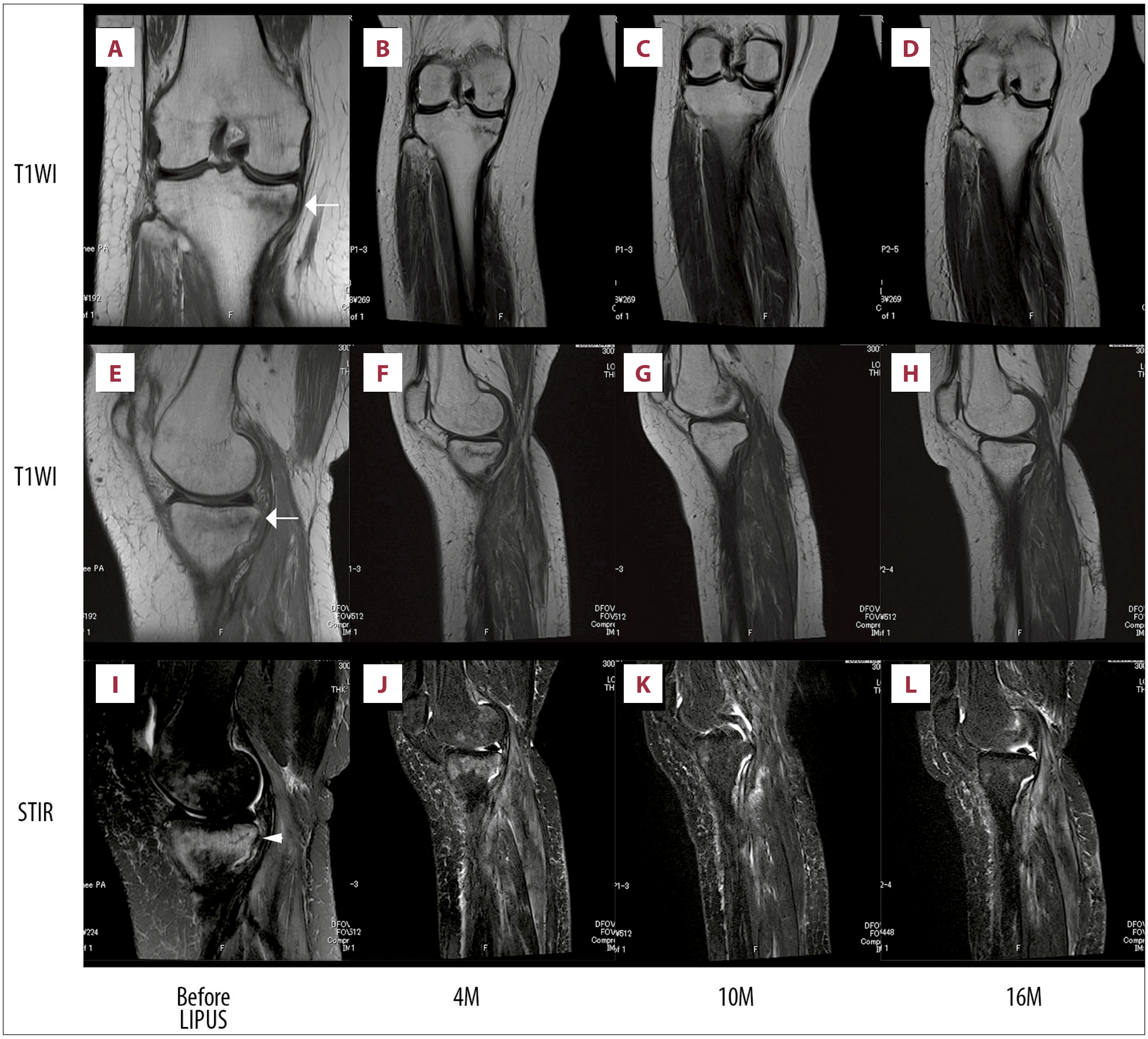


Figure 6. MRI signals and time course of the resolution for the insufficiency fracture in the proximal medial tibia. Coronal T1-weighted images (**A-D**), sagittal T1-weighted images (**E-H**), and sagittal T2-weighted images with fat suppression of the right knee taken immediately after the onset of the knee pain, and 4 months, 10 months, and 16 months after initiation of LIPUS therapy. Low signal intensity (**A and E,** arrows) on T1-weighted images and high signal intensity (**I,** arrowhead) on short TI inversion recovery (STIR) images in the proximal medial tibia disappeared over time. T1WI, T1-weighted images; STIR, short TI inversion recovery; LIPUS, low-intensity pulsed ultrasound; M, months.

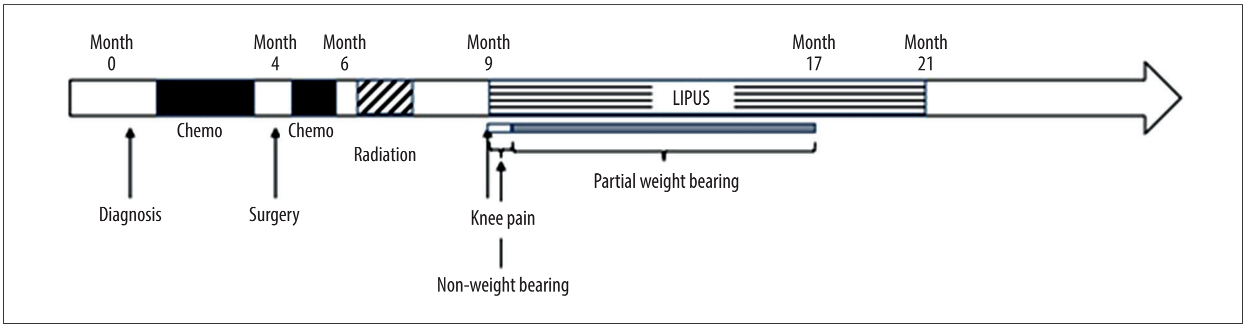


Figure 7. Timeline of our patient's clinical course. Chemo – chemotherapy; LIPUS – low-intensity pulsed ultrasound.

Indexed in: [PMC] [PubMed] [Emerging Sources Citation Index (ESCI)] [Web of Science by Clarivate]

treatment option in the management of radiation-associated fractures. To the best of our knowledge, this is the first case report describing LIPUS being used to treat a radiation-associated insufficiency fracture.

There is a potential limitation in this study. We only described 1 case and summarized our experience with therapeutic evaluation of LIPUS for insufficiency radiation-associated fracture of the tibial plateau. It is not clear whether LIPUS did decrease fracture healing time. More cases are needed to gather more therapeutic experience.

Conclusions

Clinical management of radiation-associated pathological fractures is challenging because of the high nonunion rate and potential for morbidity. LIPUS could be a safe and effective treatment option for the management of radiation-associated pathological fractures.

Acknowledgements

We appreciate the help of Drs. Yuna Inaba, Kosuke Makihara, and Masanori Hisaoka, who diagnosed the patient and obtained photographs of resected specimens and histological images. We appreciate the help of Dr. Sanshiro Inoue in the discussion section.

Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

References:

1. Dangoor A, Seddon B, Gerrand C, et al. UK guidelines for the management of soft tissue sarcomas. Clin Sarcoma Res. 2016;6:20
2. Haas RL, Delaney TF, O'Sullivan B, et al. Radiotherapy for management of extremity soft tissue sarcomas: Why, when, and where? Int J Radiat Oncol Biol Phys. 2012;84(3):572-80
3. Zagars GK, Ballo MT. Significance of dose in postoperative radiotherapy for soft tissue sarcoma. Int J Radiat Oncol Biol Phys. 2003;56(2):473-81
4. Gortzak Y, Lockwood GA, Mahendra A, et al. Prediction of pathologic fracture risk of the femur after combined modality treatment of soft tissue sarcoma of the thigh. Cancer. 2010;116(6):1553-59
5. Helmstedter CS, Goebel M, Zlotecki R, Scarborough MT. Pathologic fractures after surgery and radiation for soft tissue tumors. Clin Orthop Relat Res. 2001;(389):165-72
6. Heckman JD, Ryaby JP, McCabe J, et al. Acceleration of tibial fracture-healing by non-invasive, low-intensity pulsed ultrasound. J Bone Joint Surg Am. 1994;76(1):26-34
7. Dickie CI, Parent AL, Griffin AM, et al. Bone fractures following external beam radiotherapy and limb-preservation surgery for lower extremity soft tissue sarcoma: Relationship to irradiated bone length, volume, tumor location and dose. Int J Radiat Oncol Biol Phys. 2009;75(4):1119-24
8. Cannon CP, Lin PP, Lewis VO, Yasko AW. Management of radiation-associated fractures. J Am Acad Orthop Surg. 2008;16(9):541-49
9. Bonewald LF, Dallas SL. Role of active and latent transforming growth factor beta in bone formation. J Cell Biochem. 1994;55(3):350-57
10. Cruess RL. Osteonecrosis of bone. Current concepts as to etiology and pathogenesis. Clin Orthop Relat Res. 1986;(208):30-39
11. Azuma Y, Ito M, Harada Y, et al. Low-intensity pulsed ultrasound accelerates rat femoral fracture healing by acting on the various cellular reactions in the fracture callus. J Bone Miner Res. 2001;16(4):671-80
12. Cheung WH, Chin WC, Qin L, Leung KS. Low intensity pulsed ultrasound enhances fracture healing in both ovariectomy-induced osteoporotic and age-matched normal bones. J Orthop Res. 2012;30(1):129-36
13. Zhang R, Wang Z, Zhu G, et al. Low-intensity pulsed ultrasound modulates RhoA/ROCK signaling of rat mandibular bone marrow mesenchymal stem cells to rescue their damaged cytoskeletal organization and cell biological function induced by radiation. Stem Cells Int. 2020;2020:8863577
14. Busse JW, Bhandari M, Einhorn TA, et al. Re-evaluation of low intensity pulsed ultrasound in treatment of tibial fractures (TRUST): Randomized clinical trial. BMJ. 2016;355:i5351

Indexed in: [PMC] [PubMed] [Emerging Sources Citation Index (ESCI)] [Web of Science by Clarivate]