International Journal of Surgery Case Reports 84 (2021) 106062

Contents lists available at ScienceDirect

International Journal of Surgery Case Reports

journal homepage: www.elsevier.com/locate/ijscr

Case report

Pathologic femur fractures following surgery and radiotherapy for soft tissue sarcomas: A case series

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ARTICLE INFO

Keywords:
Soft tissue sarcoma
Pathological fracture
Fracture non-union after radiotherapy
Late effects
Case report

ABSTRACT

Introduction: Combined limb-sparing surgery and radiation therapy are considered the standard of care for higher grade soft tissue sarcomas (STS) of the extremities. The risk of post-radiation fracture after this treatment modality is well known, but still underestimated, and can end in serious long-term secondary problems years later.
Presentation of case: We reviewed the records of three patients with pathological femur fractures years after wide local excision of an STS of the proximal lower extremity. All patients received more than 50 Gy (Gy) to the entire femur circumference. During surgery, all patients had bone exposure, and in two patients with stripping of the periosteum. The median time from surgery to fracture was 116 months (range from 84 to 156 months). The median age at the time of diagnosis was 66 years old. Despite standard operative fracture treatment, all three patients developed a non-union. One patient later died due to uncontrolled pulmonary metastasis independent from the femoral non-union. In the second case, an exarticulation at hip level due to an uncontrolled infected non-union had to be performed. The third patient finally achieved fracture union after two years of treatment.
Discussion: Our study confirms the high occurrence rate of postoperative complications and difficulties one encounters in treating these pathologic fractures. Only in one patient, following several revisions with intramedullary nailing, the fracture healed. In pathologic femur shaft fractures we recommend a minimal invasive procedure using intramedullary nailing devices.
Conclusion: The risk of pathological fractures at the former treatment site is high, even years later. The rate of non-unions after a difficult fracture treatment in this particular clinical situation seems to be very high and may be associated with severe complications.

1. Introduction

Combined limb-sparing surgery and radiation therapy are considered the standard of care for soft tissue sarcomas (STS) of the extremities at least in high grade pathologies [1–3]. Using this approach, good local control can be achieved and the overall survival after STS after 5 years is around 50–60% [4]. When the tumor is close to the bone, periosteal excision may be necessary [5]. However, after this combined surgical and radio therapeutic approach, there are known complications including impaired wound healing and avascular necrosis of soft tissue and bone including pathological fractures. This holds true especially when long bones such as the femur are involved [6]. Treatment of pathologic femur fractures tends to result in a delayed- or even non-union [6].

Some studies focused on risk factors for femoral fractures after limb-sparing surgery and radiotherapy looking at the dose and extent of radiotherapy, eventual periosteal stripping or resected compartment [4,7,8]. Blaes et al. found that 8 out of 49 patients (16%) with radiation effect to 100% of the femur circumference developed a femoral fracture. [6] Time and dose of radiation seems unrelated to the risk of fracture according to Helmstadter et al. [7].

The correlation between radiation therapy and the risk of a post-radiation fracture seem to be known - at least in literature - but during the initial treatment decision making this risk might be clinically highly underestimated, especially considering the fact that it can result in serious long-term complications. The aim of this study is to present the fate of three patients with pathological femoral fractures secondary to limb-sparing surgery and radiation therapy in STS patients. All had

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https://doi.org/10.1016/j.ijscr.2021.106062
Received 7 April 2021; Received in revised form 30 May 2021; Accepted 3 June 2021
Available online 11 June 2021

extremely complicated courses and finally different outcomes. This case report has been written in line with the PROCESS 2020 guidelines [9].

2. Presentation of case

The long-term records of patients with soft tissue tumors of the thigh and subsequent pathological femur fractures treated at our institution were reviewed retrospectively. Between 2001 and 2008 three patients (two female, one male) were treated with primary limb-sparing surgery and radiation therapy for soft tissue sarcoma. They sustained a pathological femur fracture within the radiation field 7 to 13 years after the initial treatment. All procedures were performed by an experienced operator at our regional trauma center. This study is registered with the Research Registry and the unique identifying number is: researchregistry6862 [10].

Case 1 is a 41-year-old athletic male who had a myxoid liposarcoma WHO grad I at his left thigh (deep dorsal compartment). A wide excision with negative margins (R0) was performed (Fig. 1). Periosteal stripping was not necessary and the patient received 60 Gy radiation postoperatively. Thirteen years later he was injured after a low energy fall with his bike and sustained a pathologic displaced left femoral shaft fracture (Arbeitsgemeinschaft für Osteosynthesefragen [AO] 32-B2) [11]. The fracture was treated with an intramedullary stabilisation using a lateral femoral nail (LFN®, Depuy Synthes, Switzerland). Eight months postoperative, the fracture was not yet healed and non-union had to be diagnosed. As the two distal locking bolts were broken, re-stabilisation was achieved by removal of the broken bolts and relocking distally. Another 14 months later, due to a persistent hypertrophic non-union, the medullary canal was reamed again and the nail was changed to a thicker LFN®, 12 mm instead of 10 mm (Depuy Synthes, Switzerland). Two years later the fracture finally healed (Fig. 2a–g).

Case 2 is a 58-year-old female who received a wide R0 excision of a malignant fibrous histiocytoma WHO grad II at her left thigh (anterior and partially medial compartment). The operative procedure was followed by radiation therapy with 60 Gy. One year later a solitary lung metastasis was resected. Four years later a local recurrence occurred and was resected again. Another three years later a second local recurrence occurred. Once more a wide excision was performed, but this time periosteal stripping of 10 cm was necessary. A fascio- cutaneous advancement flap was used to cover the resulting defect. Unfortunately, the wound healing was disturbed by a central necrosis of the flap exposing again the femur. The patient refused the recommended new soft tissue coverage by a further operation. One year later the patient fell over a doorstep and suffered a displaced open pathologic left femoral shaft fracture (AO 32-A3) [11] at the site where the bone was uncovered for such a long time. Initial resection of dead bone, stabilisation with an external fixator and wound closure with another local flap was performed. Six weeks after initial trauma, a plate fixation with a reversed less invasive stabilisation system for distal femoral fractures (LISS-DF®, Depuy Synthes, Switzerland) was performed after bone debridement and shortening of 5 cm. Unfortunately, the patient developed an osteomyelitis and had a chronic fistula with a subsequent non-union of the fracture. Several surgical revisions over the next 4 years including the use of cement spacer, new plates and a third attempt of a soft tissue defect closure did not result in bone healing. Ultimately the patient died due to the development of an uncontrolled pulmonary metastasis and local recurrent disease. The fatal course was not directly related to the local non-union bone problem.

Case 3 In a 72-year-old female patient a wide excision of a malignant fibrous histiocytoma WHO grad III was performed (R0). The tumor was located in the anterior compartment of the left thigh. Due to almost circumferential growth of the tumor around the femur, the periosteum had to be removed to obtain sufficient safety resection margins (Fig. 3). Postoperative radiation with 66 Gy was added locally. Seven years later the patient suffered from sudden pain of the left thigh without any previous trauma. The X-ray showed a non-displaced pathologic left femoral shaft-fracture (AO 32-A2) [11]. Initially a fixation with an intramedullary nail (LFN®, Depuy Synthes, Switzerland) was performed. Due to insufficient stability and therefore no progresses in bone healing, the nail was changed twice using thicker implants after reaming of the femur. Eighteen months after the first osteosynthesis, the implant had to be changed a third time now using a reversed LISS-DF® (Depuy Synthes, Switzerland) because of a cut out of a femoral neck screw. Unfortunately, the wounds did not heal and an uncontrolled deep infection situation worsened the situation dramatically. This resulted in an exarticulation of the left leg at the hip joint performed 22 months after the first osteosynthesis (Fig. 4a–j). After that, this patient stayed in rather good shape for the next years with nearly independent personal mobility using a wheel chair.

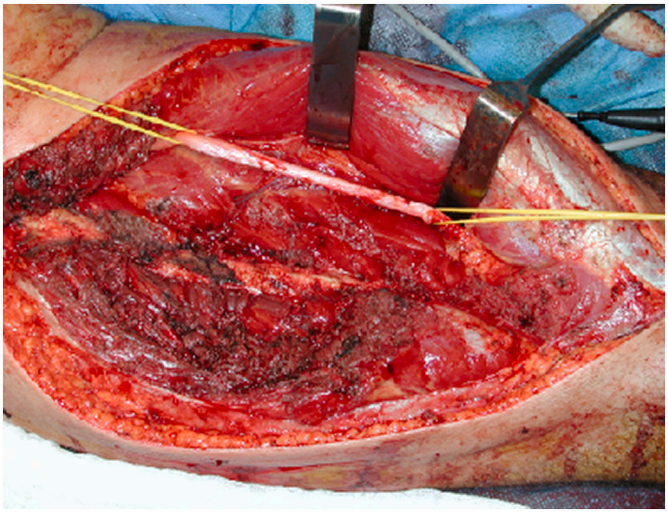

Fig. 1. Intraoperative situs presenting the deep dorsal compartment of the left femur after a wide excision. The sciatic nerve is marked.

3. Discussion

Local control rates after combined therapy with limb-sparing surgery and radiotherapy for the treatment of soft-tissue sarcomas are rather high [13,14]. However, the risk of pathologic fractures after having had radiotherapy seems to be high and their treatment poses a challenge and can be associated with severe complications even years later. This can cause physical disability and substantial impairment of the quality of life. Our study confirms the high occurrence rate of postoperative complications and difficulties one encounters in treating these pathologic fractures. Only in one patient, following several revisions with intramedullary nailing, the fracture healed. The fractures in the two other patients didn't heal even after different surgical attempts including the change of technique used and the implants. Soft tissue breakdown and infection were the major problems as a result of impaired vascularisation of the tissue after radiotherapy. The reduced bone vascularity most probably is also responsible for the delayed or non-union after fractures that seemed to occur, also without adequate trauma in a weakened bone zone of radiotherapy. This was documented in histological observations of diminished vascularity and angiogenic response to injury after irradiation [15,16]. After radiotherapy, there is often also an impairment of the function of the osteoblasts and vascular fibrosis can lead to radiation osteitis, atrophy and osteopenia [17,18].

In literature the incidence of pathologic fractures following surgery and radiotherapy for soft tissue sarcoma varies between 1.2 and 9% [5–8,19,20]. In all mentioned studies bone healing was less than 50%. Blaes et al. show an overall incidence of femoral fractures after limb-sparing surgery and radiotherapy of soft-tissue sarcomas with 9% at 10 years with increasing percentages over time [6]. Seinen et al. defined

Fig. 2. a) Pathologic left femoral shaft fracture after a low energy trauma. b) An osteosynthesis was performed using a lateral femoral nail (LFN®, Depuy Synthes, Switzerland). c) The X-ray control 8 months postoperative shows a non-union and broken screws distally. d) Re-stabilisation was achieved by a relocking distally. e) 14 months after the relocking distally the patient developed a hypertrophic pseudarthrosis. f) The medullary canal was reamed again and the nail was changed to a thicker LFN®, 12 mm instead of 10 mm (Depuy Synthes, Switzerland). g) 23 months after the second revision surgery the fracture finally healed.

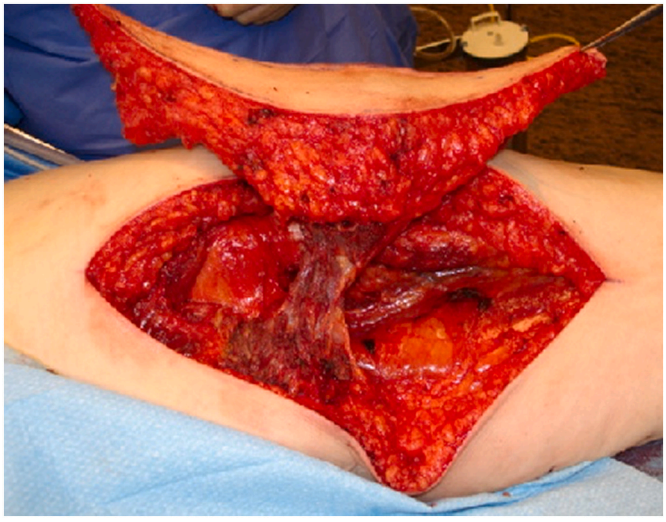

Fig. 3. Intraoperative situs presenting the left thigh. A wide excision of the anterior compartment was performed.

three independent risk factors: periosteal stripping, age > 65 years at start of treatment, and tumor size >10 cm [21]. Periosteal stripping seems to be one of the main factors [5]. Lin et al. showed that 151 out of a collective of 205 patients (73,6%) who underwent excision of a soft tissue tumor of the thigh without periosteal stripping had no subsequent fractures (0%). Whereas 9 out of 54 patients (16,7%) with periosteal stripping had pathologic fractures at the operation site [5]. Moderate or extensive periosteal stripping led to an 18-fold increase in the risk of a pathologic fracture [7]. It could clearly be shown in several papers that periosteal stripping impairs the fracture healing especially in intramedullary nailing where the endosteal blood supply is compromised [22,23]. Another possible risk factor for fractures is the location of the tumor at the thigh. Anterior compartment location of the tumor is associated with a 15-fold increase in risk according to Helmstedter et al. [7]. In our case series two out of three patients had periosteal stripping and a tumor location in the anterior compartment.

What can be done to reduce the risk of the occurrence of these fractures? Which factors can be addressed? First of all, one should minimize the dose of radiation to the normal soft tissue while maintaining adequate coverage of the target volume by intensity-modulated radiation therapy (IMRT) and proton radiation therapy [24]. Not only does it allow smaller radiation fields, but also lower doses. During the last years more and more concepts of preoperative radiotherapy are used. When compared with adjuvant radiation, the dosage can be reduced and negative side effects such as fibrosis and edema can be removed during the subsequent surgery [25]. Additionally, direct reconstructive surgery to cover the soft tissue defect can reduce the radiation side effects, such as fibrosis and therefore protecting exposed functional structures like tendons or joints from functional restrictions [25,26].

Surgical fracture stabilisation is the treatment of choice in the majority of such cases. In pathologic femur shaft fractures we recommend a minimal invasive procedure using intramedullary nailing devices as we would do in non-pathological fractures. The intramedullary nail is a load-sharing device which can bear a significant amount of load for a long period [27]. In Case 1 and 3 it was our first choice. Only in Case 2 we initially used an external fixator due to the open fracture of the chronic uncovered femur bone, followed by open plating during 2nd look surgery. Wounds within the radiated field are highly sensitive for infection and wound healing problems [6,28]. Therefore, the advantages of minimal invasive techniques have to be taken into consideration.

Han et al. [29] described a vascularized bone graft to enforce rapid union of the bone in 160 fractures with skeletal defect due to non-union, resulting from resection of a tumor, traumatic bone loss, osteomyelitis or a congenital anomaly. However, this means to expose the fracture side with increased risk of infection and also reduced blood supply due to the surgical related soft tissue damage with possible postoperative wound healing problems. As an alternative to intramedullary nailing, plates can be used for fixation. Again a wider incision in a radiated area with poor healing prospects is needed using plate fixation techniques. A higher risk of peri-implant fracture might also be considered [21]. Yet another option described in literature is the prosthetic replacement after subtrochanteric or diaphyseal fractures of the femur. It could minimize complications seen after osteosysnthesis and the need for revision surgery [30]. However only one paper compares 6 patients with prosthetic replacement retrospectively with 30 patients after internal fixations

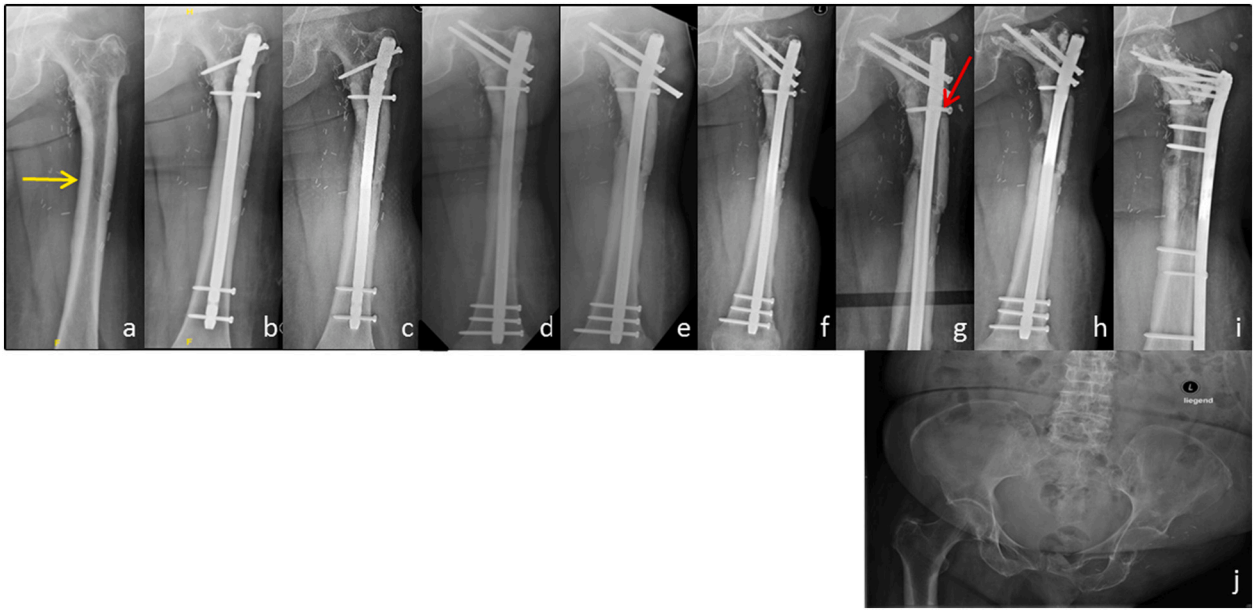

Fig. 4. a) Pathologic left femoral shaft fracture after a low energy trauma (yellow arrow). b) An osteosynthesis was performed using a lateral femoral nail (LFN®, Depuy Synthes, Switzerland). c) The X-ray control 3 months postoperative shows a delayed union due to bone healing impairment and insufficient stability. d) The medullary canal was reamed again and the nail was changed to a thicker LFN®, 12 mm instead of 10 mm (Depuy Synthes, Switzerland). e) Another 5 months later the X-ray shows a loosening of distal neck screw. f) Postoperative X-ray after changing the distal neck screw with cement-augmentation. g) Yet another 7 months later the patient developed a new intertrochanteric femoral fracture after screw and nail breakage proximally (red arrow). h) 3 months after re-nailing using a LFN® 12 mm (Depuy Synthes, Switzerland) with cement-augmentation of the neck screws, decortication and autologous cancellous bone grafting, a varisation of the head-neck-fragment with cut out and loosening of one neck screw had to be diagnosed. i) The implant had to be changed a third time. A LISS-DF® (Depuy Synthes, Switzerland) was implanted in a reversed manner after performing a closed wedge intertrochanteric valgisation osteotomy. j) Finally, due to an uncontrolled deep infection, an exarticulation of the left leg at the hip joint had to be performed 22 months after the first osteosynthesis. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

(intramedullary nailing or plate fixation) in this special clinical situation. Usually these oncological prostheses are used as a salvage procedure or after complications. In case of failures, unfortunately there is little left to do [27]. The last option remains the major amputation, especially if an infection cannot be controlled by generous bony debridement and intravenous antibiotics [27]. Also in case of a persistent non-union, when several procedures were unsuccessful, amputation may be a last option as well [31].

Because of the high risk of non-union and infections after osteosynthesis of these pathological femur fractures, prophylactic intramedullary fixation of the femur for high risk patients could be an option [32]. Helmstedter et al. suggested the fixation with intramedullary nails especially for patients with a high risk of postoperative fractures, e.g. resection of large tumors in the anterior compartment, extensive periosteal stripping and adjuvant radiation therapy [7]. It seems to be a simple procedure in the elective setting. But the interference of the implanted metal with subsequent imaging studies for detection of local recurrence might be a disadvantage [5]. In addition, timing could be crucial. Intramedullary fixation at the time of the index surgery might produce serious complications due to wound healing problems and further diminished blood supply. On the other hand, in the study of Gortzak et al., 30% of the fractures occurred within 2 years of surgery indicating that prophylactic stabilisation should not be delayed too much [32]. Cannon et al. don't recommend prophylactic intramedullary fixation, even with the above mentioned risk factors, because the overall fracture rate is too low [8].

There are limitations to this study; its retrospective nature and the small number of patients. A large number of patients and the comparison of different surgical treatments will be required to evaluate the best procedure for future treatment of these patients. Unfortunately due to the low number of cases, it is hardly feasible. One of the study's strengths is that all patients are operated on by an experienced surgeon at the same trauma center. This study highlights the challenging clinical problem that fractures of the irradiated femur have a very low potential to heal.

4. Conclusion

This case series provides three examples that illustrate the problems encountered in patients with pathological femur fracture after limb-sparing surgery and radiation therapy for soft tissue sarcoma. Local control and long term survival after combined therapy for the treatment of soft-tissue sarcoma can be achieved. But the risk of pathological fractures at the former treatment site is high, even years later. The rate of non-unions after a difficult fracture treatment in this particular clinical situation seems to be very high and may be associated with severe complications, ending in a significant impairment of the quality of life and physical disability.

Informed consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images except Case 2 due to the fatal course. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Ethical committee approval

Not required in our institution to publish anonymous case reports.

Provenance and peer review

Not commissioned, externally peer-reviewed.

Registration of research studies

1. Name of the registry: Research Registry
2. Unique identifying number or registration ID: researchregistry6862
3. Hyperlink to your specific registration (must be publicly accessible and will be checked): https://www.researchregistry.com/browse-the-registry#home/registrationdetails/60af4de8a4b8f8001e1e065b/

Guarantor

Tobias Bretschneider – Main Author

CRediT authorship contribution statement

Tobias Bretschneider: Data curation, Writing- Original draft preparation

Christian Michelitsch: Conceptualization, Methodology, Writing- Reviewing and Editing

Herman Frima: Methodology, Writing- Reviewing and Editing

Markus Furrer: Conceptualization, Writing- Reviewing and Editing

Christoph Sommer: Writing- Reviewing and Editing, Supervision

Declaration of competing interest

Tobias Bretschneider, Christian Michelitsch, Herman Frima, Markus Furrer and Christoph Sommer declare that they have no conflict of interest.

Acknowledgements

The authors thank Michelle Reynolds for the excellent copy-editing of this manuscript.

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