Referral patterns, prognostic models and treatment in soft tissue sarcomas

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Chapter 7

Fractures after multimodality treatment of soft tissue sarcomas with isolated limb perfusion and radiation; likely to occur and hard to heal

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Abstract

Objectives. Treatment associated fractures (TAFs) are known severe side effects after surgery and radiotherapy for soft tissue sarcoma (STS). There is no literature about TAF after multimodality treatment with isolated limb perfusion (ILP) for locally advanced STS. This study aimed to analyze predictive factors, treatment and outcome for TAF after multimodality treatment with ILP.

Method. Out of 126 consecutive patients undergoing ILP after 1991 till now, 25 patients were excluded due to no surgery or direct amputation at initial surgery. Therefore, 101 patients were at risk and 12 developed a TAF (12%).

Results. The majority of tumors was located at the upper leg and knee (N=60), and 11 patients developed a TAF (18%) after median 28 (5-237) months. Twenty-five tumors were located at the lower leg, and 1 patient developed a TAF after 12 months (4%). No patients with a tumor at the upper extremities (N=16) developed a TAF. Ten out of 12 patients with a fracture received adjuvant RT with a dose of 50 Gy, and a median boost dose of 18 (10-20) Gy. Predictive factors were periosteal stripping, age over 65 years at time of treatment and tumor size after ILP ≥ 10cm. Multivariate analysis showed periosteal stripping and tumor size after ILP ≥ 10cm as significant predictive factors.

The majority of the fractures were treated with intramedullary nailing. Only one of 12 patients without radiotherapy reached bone union (8%). The median survival after developing TAF was 18 (1-195) months.

Conclusion. The overall risk of TAF after multimodality treatment with ILP was relatively high with 15% at ten years. The incidence of TAF for patients with tumors located at the thigh and knee after resection with periosteal stripping and radiotherapy was even >50%. The treatment of these fractures is challenging due to the high non-union rate, requiring an extensive orthopedic oncological TAF experience.

Introduction

Since (neo-)adjuvant radiotherapy has become the standard of care in case of marginal resection margins in the treatment of soft tissue sarcoma (STS), local control rates have improved up to 80-95%. [1-5] However, due to the more frequent use of radiotherapy, the incidence of treatment related complications such as fractures has increased as well; the reported incidence ranging from 1.2 – 9%, with most fractures occurring in the femoral bone. [1, 6-10]

Radiation is believed to attribute to impaired proliferation of normal functioning osteoblasts, as well as prohibiting neo-angiogenesis in fracture healing. [11, 12] In addition, periosteal stripping has previously been reported as risk factor for fracture [7, 9, 13], which is due to the fact that disruption of the periosteum leads to a significant decrease in cortical bone perfusion. [14, 15] Although numerous studies have looked at the incidence and predictive factors of treatment associated fractures (TAF) in STS patients undergoing surgery and adjuvant radiotherapy, not much is known about the incidence and issues in STS patients with primary irresectable tumors undergoing isolated limb perfusion (ILP), delayed surgery and adjuvant radiotherapy. Due to the large size of these primarily irresectable tumors, close proximity to the bone and marginal resection margins, which often necessitates periosteal stripping and radiotherapy to ensure clear margins and good local control, there is an accumulation of risk factors for the development of treatment associated fractures (TAF). These fractures have a high non union rate and are a major cause of patient morbidity. The management of TAF is controversial. [16-18] Furthermore, there are even authors suggesting prophylactic intramedullary nail stabilization.[16-19]

The aim of this study was to look at the incidence and predictive factors of TAF in STS patients undergoing isolated limb perfusion (ILP), delayed surgery and adjuvant radiotherapy, with special regard to their local treatment and outcome. To compare incidence, predictive factors, treatment and outcome, a review of current literature was performed.

Patients and methods

The Institutional Review Board approved this retrospective study (case number 201800233).

The prospectively collected database of 126 consecutive patients undergoing ILP and delayed surgery from 1991 till now was studied. The reason for multimodality treatment with ILP was no feasible primary surgery due to large tumor size and/or close adherence to vascular or nerve structures as previously described.[20]

The median follow up after diagnosis was 64 (5-233) months, and for the survivors the median follow up was 106 (8-233) months. Seven patients were lost to follow up, one after 2 years, the other six patients after 5 years or longer.

Patient records were reviewed to corroborate the information in the database, especially with regard to the size of the tumor, evidence of bone involvement by the tumor, radiation dose, and radiation fields. The operation and histology report were used to determine whether periosteum was removed as part of the specimen.

Fracture Analysis

A treatment related fracture was considered when the following criteria were met: 1) minimal or no trauma, and 2) located at the site of the original sarcoma. A delayed union was considered to occur if there were no radiographic signs of healing at 6 months postoperatively but subsequent healing did occur with or without further surgical intervention. A nonunion was present if union had not occurred at last follow up or death, minimal one year after occurrence.

Isolated Limb Perfusion

The ILP technique has been described previously. [21, 22] After 59 ILPs, perfusion duration was shortened from 90 to 60 min, and after 75 ILPs a reduced dose of TNF was used without affecting the local treatment.[21] Currently, in axillary and popliteal perfusions 1 mg TNFα (Beromun®, Boehringer-Ingelheim GmbH, Vienna, Austria) and in iliac and femoral perfusions 2 mg TNFα is used. The dose of Melphalan (Alkeran®, GlaxoSmithKline Pharmaceuticals, Research Triangle Park, NC, USA) used in ILP is based on limb volume: 10 mg/L for lower limb perfusions and 13 mg/L for upper limb perfusions. In the first 21 ILPs, performed between 1991 and 1993, Interferon-γ (IFN-γ) was added to the schedule.

Surgery
Surgery was performed 6-8 weeks after ILP. There were no compartment resections performed as suggested by Enneking. [22] The goal was to perform a wide local R0 resection and to avoid a R2 resection. Major nerves or vessels were only resected to overcome a R2 resection, while a R1 resection was accepted. For sarcomas fixed to the bone, the periostium was stripped to ensure an R1 resection.

Radiotherapy
Postoperative external beam radiotherapy was considered indicated in case of <95% tumor necrosis with marginal resection margins, microscopically or macroscopically involved resection margins. Radiotherapy was administered in a schedule of 50 Gy with fractions of 2 Gy daily, 5 times a week, started within 6-8 weeks after surgery. In case of R0 resection, an additional boost dose of 10 Gy was administered to the tumor bed and in case of R1 resection a boost dose of 20 Gy was delivered.

From 2011 we changed the multimodality treatment scheme into ILP, pre-operative RT using 12 times 3 Gy and surgery within 2-4 weeks, with the aim to reduce overall treatment time. A total of 11 patients underwent this scheme.

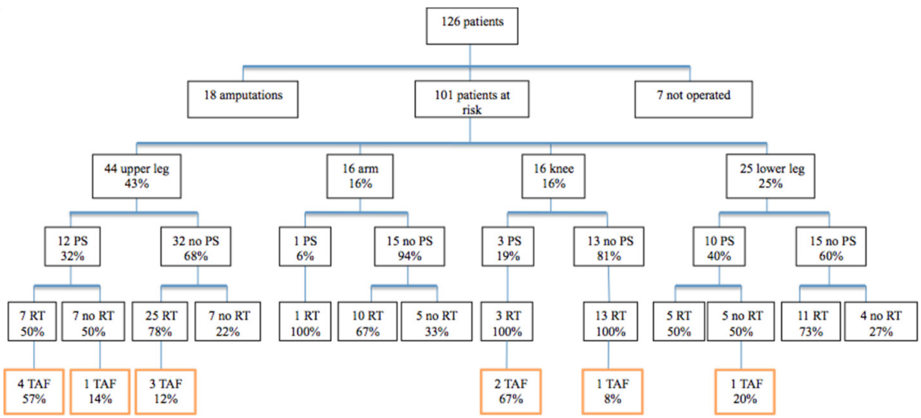
Chemotherapy
Postoperative chemotherapy was given within European Organization for the Research and Treatment of Cancer trials (EORTC 62061 and 62931) before the start of radiotherapy, or outside a trial in the palliative setting, in case of distant metastases.

Statistical analysis
The risk of fracture was determined by Kaplan Meier survivorship, because the length of follow up varied, and fractures occurred at variable times. Fractures were considered to be events. Patients were censored at the last follow up or at death. If patients required subsequent amputation for local recurrence, then the patients were censored at the time of amputation. Univariate analysis on cate-

gorical factors was performed with the log rank test. Cox multiple regression with forward, stepwise, conditional analysis was used to identify independent predictors of fracture. All analyses were performed using IBM SPSS statistical software version 22 (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp).

Results

Reviewing all 126 consecutive patients, 7 patients were excluded because they underwent no surgery after ILP, and another 18 patients were excluded because they underwent amputation at initial surgery (Figure 1). Therefore, 101 patients were identified at risk for a TAF (80%).



Abbreviations: LSS = limb saving surgery, PS = periosteal stripping, RT = Radiotherapy, TAF = treatment associated fractures

Figure 1. Overview of patients developing a treatment associated fracture

Eighteen patients underwent chemotherapy, 12 because of metastasis and 6 as part of the EORTC trial. Fourty-four patients died during the study period (44%). Twelve patients (12%) developed a TAF, after median follow up of 29 (4-236) months. One patient developed a femoral fracture after twenty years at the age of 68 years, due to standing up from a chair; she was treated with radiotherapy to a dose of 70 Gy. Patient and tumor characteristics are presented in Table 1.

Table 1. Patient and tumor characteristics			
Clinicopathologic characteristic	**Group**	**Patients at risk with TAF (n = 12)**	**Patients at risk without TAF (n = 89)**
Age at start treatment, years	Median (range)	48 (22-77)	56 (15-84)
Sex	Male	7	52
	Female	5	37
Tumor size, cm (after ILP)*	0 – 10	3	55
	≥ 10	9	34
Grade	High	10	75
	Low	2	14
Unifocal disease	Yes	8	74
	No	2	13
Primary disease	Yes	10	80
	No	2	9
Location	Arm	0	16
	Upper leg	8	36
	Knee	3	13
	Lower leg	1	24
Histological subtype	Undifferentiated pleomorphic sarcoma	3	13
	Myxoid liposarcoma	1	12
	Other	8	64
Local recurrence	Yes	1	10
	No	11	79
Radiotherapy	Yes	10	66
	No	2	23
Periosteal stripping	Yes	8	18
	No	4	70
Adjuvant Chemotherapy	Yes	2	20
	No	10	69

Abbreviations: TAF = treatment associated fracture, ILP = isolated limb perfusion
*from 4 patients tumor size not known

The majority of tumors were located at the upper leg (n=44), of which 12 patients underwent periosteal stripping, 32 received adjuvant radiotherapy and 7 patients underwent both periosteal stripping and adjuvant radiotherapy (Figure 1). Patients undergoing both periosteal stripping and radiotherapy had the highest fracture risk, respectively 57% of patients with tumors located at the upper leg, and 67% located at the knee. Two of these patients with tumors at the upper leg received RT twice for a primary tumor as well as for a local recurrence, with overlapping radiation field. One patient with a tumor of the thigh developed a TAF without receiving adjuvant radiation, but after periosteal stripping and resection of the anterior lateral muscle group.

Of the remaining patients at risk for TAF, 25 had a tumor located at the lower leg, and 1 developed a TAF after receiving periosteal stripping. None of the patients with tumors located at the arm developed a TAF.

Risk factors for fractures

The risk of fracture for the total cohort of 101 patients at 5 and 10 years was 12% and 15% respectively. Univariate analysis showed three risk factors with statistically significance for the development of TAF (Table 2): periosteal stripping (p = 0.002), age ≥ 65 years at start of treatment (p = 0.002) and tumor size ≥ 10 cm after ILP (p = 0.003). Continuing with multivariate analysis, tumor size ≥ 10 cm after ILP (p = 0.013) and periosteal stripping (p = 0.018) remained independent significant negative predictive factors of TAF.

Ten out of twelve patients with a fracture received adjuvant RT, which consisted of a complete radiation schedule of 50 Gy, with a median boost dose of 18 (10-20) Gy. All fractures developed in the booster area. Nevertheless, RT was not a risk factor for development of fractures at ten years (p = 0.755).

Treatment and outcome

Seven out of ten patients with a femoral fracture were initial treated with intramedullary nailing, two patients were treated with plate fixation and one with a cast (Table 3).

Table 2. Univariate analysis: Risk factors and development of treatment related fractures (at five and ten years)				
Clinicopathologic characteristic	**Group**	**Kaplan Meier risk of TAF at 5 years (%)**	**Kaplan Meier risk of TAF at 10 years (%)**	***P* – value**
Periosteal stripping	Yes	27	36	
	No	5	7	0.002
Age at start treatment, years	< 65	8	13	
	≥ 65	17	17	0.002
Tumor size, cm (after ILP)	< 10	3	3	
	≥ 10	21	33	0.003
Sex	Male	10	19	
	Female	11	11	NS
Radiation	Yes	10	15	
	No	13	13	NS
Radiation dose booster (Gy)	Yes	9	14	
	No	14	14	NS
Grade	High	12	17	
	Low	6	6	NS
Unifocal disease	Yes	11	16	
	No	8	8	NS
Primary disease	Yes	11	16	
	No	9	9	NS
Location	Upper leg	17	28	
	Lower leg	5	5	
	Knee	12	12	
	Arm	0	0	NS
Chemotherapy	Yes	12	12	
	No	10	15	NS

Abbreviations: TAF = treatment associated fracture, ILP = isolated limb perfusion, UPS = undifferentiated pleomorphic sarcoma, NS = not significant

Table 3. Treatment and outcome for patients with treatment associated fractures					
P	**Time to TAF (months)**	**Age at diagnosis (years)**	**Location**	**Treatment**	**Follow up**
No adjuvant radiotherapy					
1	36	22	Femur	Plate fixation	No re-operation
2	12	51	Tibia	Amputation	No re-operation
Adjuvant radiotherapy					
3	224	63	Distal femur	Intramedullary nail	LISS-plate (insufficient stabilization)
4	95	65	Femur	Intramedullary nail	No re-operation
5	237	68	Femur	Plate fixation	New DCS plate after taking out LISS plate due to pseudoathrosis and breaking plate
6	67	50	Femur	Intramedullary nail	- Intramedullary fixation (broken nail) - Intramedullary fixation (broken nail) - Resection prox. femur and reconstruction with a prosthesis (broken nail)
7	5	64	Femur	Intramedullary nail	Additional screws (broken nail)
8	5	72	Distal femur	Cast	Intramedullary fixation
9	6	72	Femur	Intramedullary nail	No re-operation
10	28	77	Femur	Intramedullary nail	No re-operation
11	28	47	Femur	Intramedullary nail	No re-operation
12	7	65	Tibial plateau	No operation	No operation

Abbreviations: P = patient, TAF = treatment associated fracture, DFN = distal femural nail, LISS = less invasive stabilization system, n.a. = not applicable, NED = no evidence of disease, DOD = death of disease, AWD = Alive with disease

One patient (nr 2 in Table 3) with a tibia fracture had a concurrent non healing post radiation wound which necessitated an amputation. Only one patient out of the eleven patients undergoing limb salvage treatment reached consolidation of the bone after one year. In the follow up, four patients needed re-operation due to insufficient stabilization or broken intramedullary nails. One patient had three broken nails and received eventually a reconstruction with a tumor endoprosthesis (Figure 2). In one patient a conservative treatment with a cast was unsuccessful and eventually intramedullary nailing was performed. To evaluate the mobility after treatment we reviewed the patient charts. Most patients had impaired mobility, and needed support from crutches. Three patients have reasonable mobility without support. One patient has moderate mobility due to pseudoarthrosis as consequence of the internal fixation, but refused tumor prosthesis.

Union	Mobility	Overall survival after TAF (months)	Status
Yes, delayed	Normal	195	NED
n.a.	n.a.	10	DOD
No	> 1h walking without pain, normal function	8	NED
No	Max 10m, due to pain (athrosis)	126	NED
No	Mobile with walker	56	NED
No No	No mobility problems due to prosthesis, some functional limitations due to resection of muscles	110	NED
n.a.			
No	Max 50m with crutches	13	DOD
No	Mobile with crutches	19	DOD
No	n.a. (early death)	1	DOD
No	Mobile with crutches	10	NED
No	Mobile with crutches	24	AWD
No	Mobile with crutches	16	AWD

The median survival after TAF was 18 (1-195) months, with four patients dying due to lung metastases within 1.5 years. Of the remaining eight patients, six are free of disease and two are alive with metastasis.

Review of literature

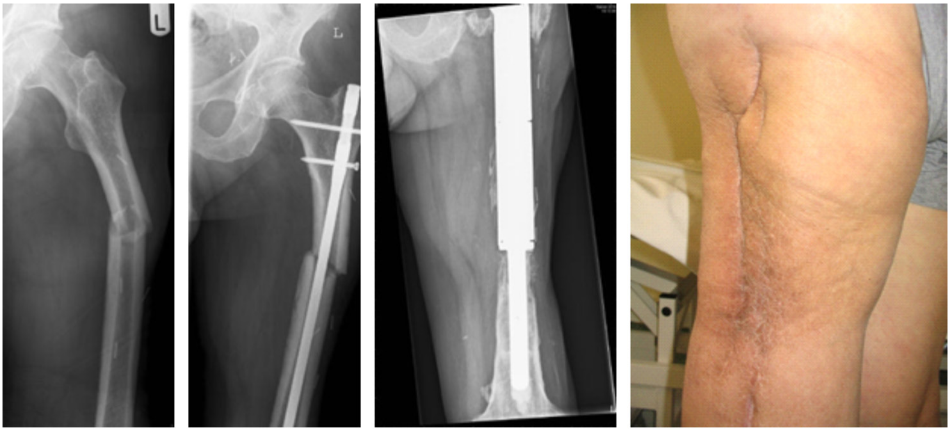
We performed a review of the literature and searched for studies about treatment associated fractures after surgery and radiotherapy for soft tissue sarcomas (Table 4). [6, 8-10, 13, 23, 24] None of these studies included ILP. The incidence of TAF varied from 1.2 – 9%. Two studies performed multivariate analysis and reported a high radiation dose (≥ 60 Gy), periosteal stripping, gender and age (> 55 years) as independent prognostic factors. All studies reported a low percentage of <50% (delayed) bone union.

Table 4. Review of literature: incidence, treatment and outcome

Study	Time to fracture (years)	Incidence of TAF (%)	Univariate: Risk factors
Lin et al. 1998* [9]	2 (mean)	9/205 (4.4)	Periosteal stripping Tumor location (anterior) Gender (Female) Chemotherapy Age (≥50years) Radiation type (external)
Helmstedter et al. 2001 [13]	3.4 (mean)	20/285 (7)	Periosteal stripping Tumor location (anterior)
Holt et al. 2005** [8]	3.4 (median)	27/364 (7.4)	High dose (≥60 Gy) Gender (female) Age (> 55 years)
Cannon et al. 2006** [6]	5.2 (median)	5/412 (1.2)	Periosteal stripping Femur circumference in RT field (100%)
Kim et al. 2010 [23]	3.5 (mean)	39/1045 (3.7)	-
Blaes et al. 2010* [10]	13 (median)	8/89 (9)	Periosteal stripping Femur circumference in RT field (100%) Tumor location (anterior)
Bishop et al. 2016* [24]	40 (median)	12/596 (2)	Periosteal stripping Femur circumference in RT field (100%) Perioperative bone exposure Perioperative chemotherapy
Seinen et al. 2017 *Current series*	29 (median)	12/101 (12)	Periosteal stripping Age (>65 years) Tumor size (>10cm)

*Tumor located at femur, **Tumor located at lower extremity
Abbreviations: TAF = treatment associated fracture, RT = radiotherapy, IM – intra medullar, ORIF = open reduction and internal fixation

Multivariate: Risk factors	Treatment	Outcome
Periosteal stripping	7 unknown 1 primary endoprosthetic replacement 1 primary amputation	3 delayed union 4 non union
-	10 nails (IM, other) 1 prosthesis 7 casts 2 immobilization	4 delayed union 9 non union 5 union
High dose (≥60 Gy) Gender (female) Age (> 55 years)	-	-
-	-	-
-	30 ORIF 6 prosthetic replacement	19 non union 11 union
-	-	3 delayed union 2 non union 3 union
-	-	-
Periosteal stripping Tumor size (>10cm)	2 plate fixation 7 Intramedullary nail 1 amputation 2 conservative	10 non union 1 delayed union (1 amputation)



A B C D

Figure 2. Patient with a TAF of the thigh (nr 5 of Table 3). Femoral fracture (A), Intramedullary nailing (B), Tumor prosthesis (C), Follow up result (D)

Discussion

The extensive combined modality treatment for locally advanced soft tissue sarcoma patients has provided an alternative for amputation, with 80-86% long term limb salvage with good functional outcome and overall survival.[25] The local recurrence rate in the current study population undergoing limb salvage surgery (n=101) was only 11%, in spite of large tumor sizes. The distant metastases rate was 46%. The incidence of metastasis in patients treated for locally advanced STS is 36 – 43% [26, 27, 28] and most of these patients eventually die due to their disease. Nevertheless, this extensive treatment can cause severe long term morbidity, e.g. TAF, which results in impaired functional outcome.

A unique series of TAF is described after ILP, surgery, periosteal stripping and/or radiotherapy, with an overall risk of TAF at ten years of 15%. The incidence of TAF was high (12%). When only patients with tumors of the thigh were considered, the incidence was even as high as 22%. But the highest incidence was found in patients with tumors located at the thigh and knee who underwent both periosteal stripping and radiotherapy (>50%). Compared with previous reported incidences of 1.2 – 9% [6, 8-10, 13, 23, 24] of studies analyzing patients undergoing only surgery and radiotherapy, the incidence of a pathological fracture is substantially higher after multimodality treatment including ILP. Which is at least partially explained by the treatment indication of ILP for large tumors, precipitating extensive resection of muscles, high risk of periosteal stripping and larger radiation fields. In addition, TNF alpha and Melphalan have effect on osteoclast activity, thereby possibly contributing to the higher risk of TAF. Melphalan modifies the bone microenvironment by stimulating the formation of osteoclasts. [29] TNF alpha is a cytokine involved in the regulation of osteoclast activity, promoting bone resorption via a primary effect on osteoblasts. [30]

Moreover, patients undergoing multimodality treatment with ILP seem to develop TAF in a shorter follow up time (median 2.7 years) compared with patients not undergoing ILP (mean 2 – 3.5 years, median 3.4 –13 years). [6, 8-10, 13, 23, 24] Another large study analyzing outcome after ILP did not report TAF's, which could be due to a shorter follow up (29 vs 64 months) and other primary end points of the study. [27]

In accordance with previously published studies we found periosteal stripping and age ≥ 65 years as predictive factors of TAF. [6, 8-10, 13] The amount of stripping could not be measured quantitatively. The significant association between size and fracture could implicate that the amount of stripping may have been therefore, roughly proportional to the size of the tumor.

Tumor size ≥ 10 cm and periosteal stripping were the only independent significant predictive factors in multivariate analysis in this study, of which tumor size has previously not been reported as predictive factor. This is not surprising since the patients in this study were undergoing ILP due to their irresectable nature, which is mostly due to their large tumor size. Two reasons could underlie the association between size and fracture risk, first of all, the radiation field is based on the tumor size and resection area, and secondly, a large tumor is more likely to have close adherence to the bone which necessitate periosteal stripping. Other factors such as tumor location (anterior), female gender and femur circumference in RT field have previously been suggested as negative predictive factors for TAF. [6, 8-10, 13, 23, 24] Female gender has been related to increased risk fracture due to concurrent diminished bone mineral density after menopause. In this study the age of the women with fractures was relative low (median 57 years) compared to men (median 72 years), which could explain why no difference for gender was found.

In this study, radiotherapy was not a significant predictive factor at ten years for fracture. Separate analysis were performed regarding; pre- vs postoperative RT, booster (70 Gy) vs no booster (60 Gy) and tumor location, however this did not affect outcome (data not shown). However, there is epidemiological evidence that links radiation to pathological fractures. [6-10, 13] Also, there are histological observations of decreased osteocyte number, suppressed osteoblastic activity, and diminished vascularity in tissue of patients who underwent radiotherapy. [11, 12] Moreover, irradiated bone shows diminished angiogenic response to injury due to abnormal vascularity. [11, 12] A possible explanation is that two patients developed TAF's without radiotherapy, comprising 17% of the total number of patients with TAF's.

Most likely, it is the combination of several factors that induce vulnerability of the bone. Diminished muscle mass, which results from surgical excision also plays a role by increasing and changing the loading forces on bone and exacerbate fatigue damage, which was the likely mechanism behind the fracture of one patient in this study who did not receive radiotherapy.

Most of the factors that increase the risk of TAF are impossible to eliminate. But new developments of radiation techniques, e.g. intensity-modulated radiation therapy (IMRT) and proton radiation therapy, might achieve minimizing the dose to the surrounding normal soft tissue while maintaining adequate coverage of the target volume [31], thereby lowering the total dose to the bone. In addition, new treatment schedules with pre-operative radiotherapy, which allows smaller radiation fields and lower doses, could also lower the risk for TAF. The long term results of these treatments have to be awaited.

Moreover, sarcoma specialists now rise the question if radiotherapy should have a standard role in the multimodality setting, since Deroose et al have shown that good response to ILP (>50% tumor necrosis) followed by R0 resection have low risk of recurrence and radiotherapy does not add further benefit. [32,33]

Continuing in the perspective of pre-operative RT, direct reconstruction with plastic surgery could reduce late radiation effects, such as fibrosis. This procedure is of major interest in cases of exposed functional structures, such as tendons or joints where fibrosis and edema can compromise functional restrictions, thereby changing weight load and adding to a higher risk fracture. [34, 35]

One of the few preventive measures for osteoradionecrosis is hyperbaric oxygen therapy, of which the positive effect has mainly been analyzed at the location of the jaw. [36] The basic principle of this technique is that it induces neovascularization and reduces fibrosis in radiated hypoxic tissues. Also part of the patients benefit of this technique in case of soft tissue wound healing problems. If this treatment could also help to induce union for TAF after multimodality treatment in soft tissue sarcomas, is not yet analyzed.

The diagnosis of TAF can sometimes be made on plain radiographs, however additional imaging with magnetic resonance imaging can be helpful to detect early stress fracture or even a possible recurrent disease. [37,38] The additional value of a biopsy is arguable because of the high probability of osteonecrosis and the low diagnostic efficacy. [16]

Treatment of patients with TAF after extensive therapy with ILP, delayed surgery – especially including periosteal stripping – and RT is challenging. Given the high rate of non union, generally > 50% [9, 10, 13, 23], and the often long time before consolidation is reached, surgical treatment is indicated in the majority of cases. Yet, these patients are highly sensitive for infection and wound healing problems. [10, 21, 28] Therefore, fractures of the long bones should preferably be treated with minimal surgery like intramedullary (IM) nailing. It is important for the treating physician to realize that this type of fracture is not a normal fracture. The tendency to heal is extremely low and repetitive nailing in case of refracture or non union is contraindicated. The fixation should not be removed at a later date because the likelyhood of refracture is high. The advantages of IM nailing is a small incision, and a long nail can support the total area of osteonecrosis. The disadvantage is that TAF's have a high risk of non – or delayed – union, and the IM nail has to bear the load forever. [39] There is heavily impaired bone healing and one cannot rely on normal fracture healing concepts. Indeed, three patients in this study needed revision surgery after IM nailing due to broken nails or insufficient stabilization. To enhance rapid union of bone, hyperthrophy of the bone and less resorption of cortical bone, a vascularized bone graft is sometimes used [40], however, this does imply a larger incision with an increased risk of infection and wound healing problems. The quality of the host vessels can be impaired due to ILP, RT and progressed age. Therefore, we would not recommend to use supplemental bone grafting in case of union failure after IM nailing. An alternative is plate fixation, but this involves a wider incision in an irradiated area with poor healing properties and a higher risk of fracture outside the plate.

Not much is known about the difference in outcome between prosthetic replacement and less invasive surgery. A retrospective study of Kim et al. analyzed the difference in outcome for patients undergoing open reduction and internal fixation (ORIF) and prosthetic replacement. [23] For the ORIF technique they used both plates and IM nailing. They found that patients undergoing ORIF had significantly more complications and needed more revision surgery. If this was mainly true for the patients undergoing plate fixation or IM nailing is not clear from the article. Since the infection rate is generally high and prosthetic replacement involves an extensive challenging surgery due to a fibrotic surgical area after previous treatment, we recommend to save prosthetic replacement for those long survivors that require revision surgery due to insufficient stabilization, broken material or in case of painful non union. The exposure should preferably be done via a different approach leaving the radiated skin intact.

In this series, only one patient with TAF underwent amputation, the other patients underwent in most cases invasive treatment with plate fixation or intramedullary nailing. Resulting in some cases in reasonable functional outcome and in other cases in impaired functional outcome with the need of walking aids. Nevertheless, these patients did not wish for amputation and prosthesis.

Conclusion

Over one out of ten patients treated with ILP, surgery and radiotherapy for primarily irresectable soft tissue sarcomas of the limb developed a TAF. Patients with tumors located at the thigh or knee, undergoing both radiotherapy and periosteal stripping, have the highest risk, more than half developed a TAF. TAF is a pathological fracture with a union rate as low as 8%. Treatment of TAF's is challenging and should be performed in dedicated sarcoma centers.

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PART IV

Angiosarcoma