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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 ≥10 cm. Multivariate analysis showed periosteal stripping and tumor size after ILP ≥10 cm 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 to 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 neoangiogenesis 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

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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 Medical 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 categorical 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 (Fig. 1). Therefore, 101 patients were identified at risk for a TAF (80%). 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.

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 (Fig. 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

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