

# Hypofractionated preoperative radiotherapy for high risk soft tissue sarcomas in a geriatric patient population

Vlatko Potkrajcic<sup>1</sup>, Frank Traub<sup>2,3,4</sup>, Barbara Hermes<sup>2,5</sup>, Marcus Scharpf<sup>2,6</sup>, Jonas Kolbenschlag<sup>2,7</sup>, Daniel Zips<sup>1, 8</sup>, Frank Paulsen<sup>1,2</sup>, Franziska Eckert<sup>1,2,8</sup>

<sup>1</sup> Department of Radiation Oncology, Eberhard-Karls-University Tuebingen, Tuebingen, Germany

<sup>2</sup> Centre for Soft Tissue Sarcoma, GIST and bone tumours, Eberhard-Karls-University Tuebingen, Tuebingen, Germany

<sup>3</sup> Department of Orthopaedics and Traumatology, University Medical Center Mainz, Johannes Gutenberg-University Mainz, Mainz, Germany

<sup>4</sup> Department of Orthopaedic Surgery, Eberhard-Karls-University Tuebingen, Tuebingen, Germany

<sup>5</sup> Department of Medical Oncology, Eberhard-Karls-University Tuebingen, Tuebingen, Germany

<sup>6</sup> Institute for Pathology, Eberhard-Karls-University Tuebingen, Tuebingen, Germany

<sup>7</sup> Department of Hand-, Plastic, Reconstructive and Burn Surgery, Eberhard-Karls-University Tuebingen, Tuebingen, Germany

<sup>8</sup> German Cancer Consortium (DKTK) Partnersite Tuebingen, German Cancer Research Center (DKFZ), Heidelberg, Germany

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Correspondence to: Franziska Eckert, M.D., Department of Radiation Oncology, Eberhard-Karls-University of Tuebingen, Hoppe-Seyler-Str. 3, D-72076 Tuebingen, Germany. E-mail: franziska.eckert@med.uni-tuebingen.de

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**Background.** Standard therapy for localised, resectable high risk soft tissue sarcomas consists of wide excision and radiotherapy over several weeks. This treatment schedule is hardly feasible in geriatric and frail patients. In order not to withhold radiotherapy from these patients, hypofractionated radiotherapy with 25 Gy in 5 fractions was evaluated in a geriatric patient population.

**Patients and methods.** A retrospective analysis was performed of 18 geriatric patients with resectable high risk soft tissue sarcomas of extremities and thoracic wall. Wound healing and short term oncologic outcome were analysed. In addition, dose constraints for radiotherapy of the extremities were transferred from normofractionated to hypofractionated radiotherapy regimens.

**Results.** Feasibility was good with 17/18 patients completing treatment as planned. Wound healing complication rate was in the range of published data. Two patients developed local and distant recurrence, two patients isolated distant recurrences. No isolated local recurrences were observed. Keeping the constraints was possible in all cases without compromising the coverage of the target volume.

**Conclusions.** Hypofractionated radiotherapy and surgery was well tolerated even in this specific patient population. With feasibility concerning early wound healing problems and adapted constraints, which allow for the treatment of most resectable extremity tumours, the concept warrants further evaluation in patients unfit for standard radiotherapy.

Key words: sarcoma; radiotherapy; preoperative; geriatric patients; wound healing; hypofractionation

## Introduction

Standard treatment for localised high risk soft tissue sarcomas (subfascial, large tumours with in-

termediate or high French Federation of Cancer Centers Sarcoma Group [FNCLCC] grading) consists of wide excision plus radiotherapy over approximately 5 weeks preoperatively or 6–7 weeks

postoperatively.<sup>1</sup> This results in a treatment period of approximately 12 weeks, including the recovery phases after radiation or wound healing before the adjuvant radiotherapy. In select cases and at specialized centers chemotherapy and / or locoregional hyperthermia are added.<sup>2-4</sup> With this approach, local control is rather high for extremity tumours reaching 90%.<sup>5</sup> Oncologic outcome is mostly determined by distant metastases, especially in the lungs.<sup>6</sup>

This standard approach is almost not feasible in geriatric, frail patients with daily appointments at the radiotherapy department over 5–7 weeks and an overall treatment time of approximately three months, rehabilitation not included. Thus, radiotherapy is omitted in this patient population in a large proportion of cases. Even in patients over 65 years of age, 20% did not receive radiotherapy.<sup>7,8</sup> For geriatric patients, hypofractionated radiotherapy (with or without stereotactic treatment approaches) has been proposed as a feasible option.<sup>9</sup>

For localised high risk soft tissue sarcoma, different radiotherapy fractionations have been reported as summarized by Haas *et al.*<sup>10</sup> For example, in analogy to hypofractionated regimens in rectal cancer, a fractionation of 25 Gy in 5 fractions on consecutive days has been used.<sup>11</sup> A retrospective analysis of 272 patients describes local recurrences in 19% of patients with 7% of patients developing toxicities requiring a second surgery.<sup>12</sup> For the subgroup of myxoid liposarcoma local recurrence rate was even lower.<sup>13</sup> 25 Gy in 5 fractions in combination with chemotherapy has been reported as a phase 2 trial protocol.<sup>14</sup> The advantage for geriatric patients is the significantly reduced overall treatment time and the limited daily visits to the radiation oncology department making it more feasible as an outpatient treatment. Thus, radiotherapy is an option even in frail geriatric patients who otherwise would undergo surgery alone due to the high burden of daily visits to radiation treatment units over several weeks.

With altered radiotherapy fractionation regimens, normal tissue constraints developed for normofractionated radiotherapy with doses of 1.8 Gy to 2.0 Gy per fraction have to be revisited or newly developed. Especially with higher doses per fraction such as used in stereotactic radiotherapy, dose constraints have to be reconsidered.<sup>15</sup>

The aim of this study was to assess the feasibility concerning completion of treatment and early wound healing after preoperative hypofractionated radiotherapy for high risk soft tissue sarcomas in a geriatric patient population. In addition, dose

constraints for radiotherapy of sarcomas of the extremities have been transferred from normofractionated radiation schedules to hypofractionated treatment.

## Patients and methods

Starting in 2018, hypofractionated preoperative radiotherapy was introduced at our institution for geriatric patients with newly diagnosed high risk soft tissue sarcomas with an indication for additive radiotherapy (large, deep seated, intermediate or high grade tumours) not eligible for normofractionated (neo) adjuvant radiotherapy over several weeks. In 2020 the regimen was introduced in the second center which included patients in the analysis. All geriatric patients (> 75 years, frail, not eligible for normofractionated radiotherapy) treated with 25 Gy in 5 fractions for preoperative radiotherapy were included in this analysis. The analysis was approved by the Ethics Committee of both centers (508/2020 BO).

Eighteen patients presenting with large soft tissue masses suspicious of soft tissue sarcoma underwent biopsy of the lesion and staging with at least computed tomography (CT) of the lungs and local contrast enhanced magnetic resonance imaging (MRI) or CT after confirmation of the diagnosis. After surgical and anaesthesiological evaluation of the patients, the treatment schedule was discussed in a multidisciplinary tumour board including confirmation that patients were unfit for normofractionated radiotherapy. Given the resectability of the tumour and the operability of the patient, preoperative hypofractionated radiotherapy was offered to the patients. Surgery was planned approximately 3–4 weeks after completion of radiotherapy. Additional preoperative imaging between the end of radiation therapy and surgical resection was not obligatory. However, preoperative staging was carried out in selected cases. In order to limit the loss of quality of life and avoid complications of hospitalization for geriatric patients, most radiotherapy treatments were planned and performed on an outpatient basis.

Radiation treatment planning was performed after informed consent by the patient and/or the legal guardian. 3D conformal radiotherapy as well as intensity modulated radiotherapy (IMRT) was planned based on a planning CT with individual patient positioning depending on the anatomical localisation of the sarcoma. Target volume delineation followed the recommendations for radiother-

apy of high risk soft tissue sarcomas.<sup>16</sup> The gross tumour volume (GTV) was contoured on the planning CT by the aid of diagnostic contrast-enhanced MR and / or CT imaging. In most cases a clinical target volume (CTV) was created with a margin of 3 cm around the GTV in a longitudinal direction and 1.5 cm in a radial direction in case of extremity sarcomas. The CTV was corrected for anatomical borders. The planning target volume (PTV) margin was chosen between 0.5 and 1.0 cm according to the expected positioning precision.

Dose prescription followed the respective International Commission on Radiation Units and Measurements (ICRU) recommendations. For the coverage of the target volume a dose of 95%–107% of the prescribed dose was aimed at for the GTV. The PTV was to be covered with dose to 98% of the contoured volume (D98)  $\geq$  90% and dose to 2% of the contoured volume D2  $\leq$  107% of the prescribed dose, respectively. Most patients were treated with 3D conformal radiotherapy (n = 15). In case of better sparing of organs at risks (OARs) IMRT techniques were used, mostly volumetric arc therapy (VMAT), n = 3. Radiation planning parameters were recorded for seven patients with lower extremity sarcomas. For two patients with lower limb sarcomas radiotherapy planning parameters are missing. Analysis was focussed on lower extremity sarcomas as these pose the highest risk for pathologic fractures after radiotherapy and the published dose constraints also were limited to lower extremity. D98 was recorded for GTV and CTV. Dose constraints were evaluated according to the re-calculated constraints. The whole femur and tibia were contoured for the analysis of constraints for bone concerning pathologic fractures for thigh and calf tumours, respectively.

Surgical approaches also had to be tailored to the specific patient population of elderly and frail patients. Wide resection taking into account resulting functional deficits or the resulting necessity of plastic surgery was omitted in select cases accepting R1 or even R2 resection if patients would have been endangered with more radical surgical procedures.

Local MRI examinations (or CT for not MRI-eligible patients) and lung imaging were carried out during the follow-up. Clinical and pathological data were collected and analysed. Resection status as well as percentage of vital cells in the surgical specimen was recorded. Wound healing complications were recorded and graded according to the need for additional surgical interventions during the postoperative period.

Statistical analysis was performed with IBM SPSS Version 26 and GraphPad Version 8. Means were compared by two-sided Student's t-test. Survival times were estimated with the Kaplan Meier method. Correlations of continuous variables were described using Pearson correlation coefficients. Chi-square test was used to describe correlations between categorized variables.

## Results

### Patient population

Median patient age was 83.7 years (range 79.4–91.4 years). All patients included showed at least two features of high risk soft tissue sarcomas (subfascial localisation, intermediate or high grading according to FNCLCC or size > 5 cm). All tumours were located in extremities or superficial trunk wall, no retroperitoneal sarcomas were included. The most common histology was undifferentiated sarcoma, not otherwise specified (NOS). All patients had undergone biopsy for histopathologic confirmation of the diagnosis and had been staged with CT of the lungs prior to therapy to exclude pulmonary metastases. An overview of the patients is provided in Table 1. General condition and frailty of patients were assessed interdisciplinary with surgeons, anaesthesiologists and radiation oncologists. In case patients with extremity and superficial trunk wall sarcomas were not fit for several weeks of treatment or patients and legal guardians would have declined radiotherapy at all in case of five week treatment, hypofractionated irradiation was offered as an alternative.

### Feasibility

All patients finished the five planned radiotherapy sessions. No radiation toxicity > grade 1 (Common Terminology Criteria for Adverse Events [CTCAE] V4.0) was observed. All but one patient underwent wide resection after a median of 29 days (range 15–45 days) after end of radiotherapy. One patient deteriorated in the Eastern Cooperative Oncology Group (ECOG) performance status after radiotherapy. Thus, the patient and the legal guardian opted against moving forward to surgery and preferred a best supportive care strategy which left the patient with a good palliative radiotherapy treatment. All patients undergoing surgery were released from hospital, 30 day mortality rate after surgery was 0%. Five of 17 patients undergoing surgery de-

TABLE 1. Patient characteristics and postoperative complications

Age at diagnosis	Localisation	Size [cm]	Histology	Grading	Days to resection	Resection status	Postoperative complication	Follow up
85	forearm	7.5	NOS	2	45	1	hematoma	alive, NED
91	lower leg	5.4	NOS		no surgery			lost to follow up
82	thigh	7.0	myxofibrosarcoma	2-3	25	0		alive, NED
84	forearm	6.0	epithelioid myxofibrosarcoma	3	18	0		alive, NED
91	thigh	5.5	NOS	3	15	2		local and distant recurrence
79	thoracic wall	7.7	liposarcoma	2	29	0		alive, NED
80	gluteus	10.0	NOS	3	30	0		alive, NED
84	thigh	3.7	leiomyosarcoma	3	34	0		alive, NED
83	thigh	10.0	liposarcoma	3	21	1	wound healing complication	local and distant recurrence
80	thigh	8.0	NOS	3	31	0	wound healing complication, seroma	alive, distant recurrence lower leg, curative treatment
90	thigh	8.5	leiomyosarcoma	2	29	0	wound healing complication	alive, NED
85	axilla	9.2	liposarcoma	2	31	1		alive, NED
82	thigh	17.0	liposarcoma	2	23	0		alive, NED
87	thoracic wall	5.0	NOS	3	20	0		alive, NED
82	thoracic wall	9.0	NOS	3	23	0	wound healing complication	alive, NED
91	upper arm	5.2	NOS	3	31	0		distant recurrence
81	thigh	8.3	myxoid fibrosarcoma	3	31	0		alive, NED
81	upper arm	8.3	NOS	2	32	0		alive, NED

NED = no evidence of disease; NOS = not otherwise specified

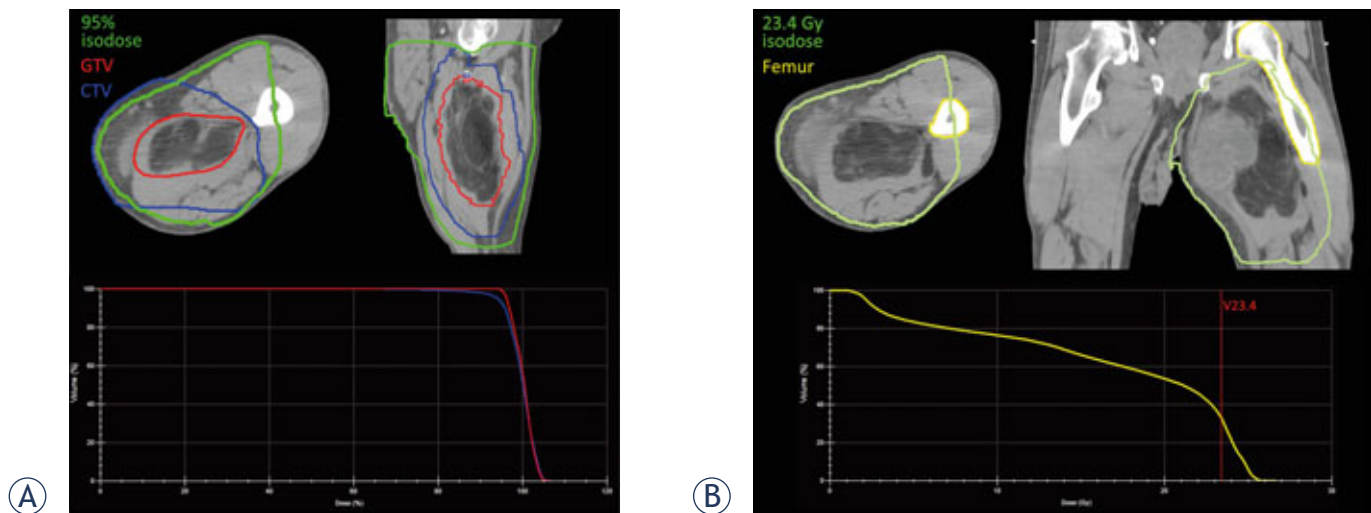


FIGURE 1. Example of a radiation plan for a thigh sarcoma. The 3D conventional radiotherapy plan shows a good dose coverage for the target volumes (even for this case of the largest tumour in our series with 17 cm) (A). The dose constraints for bones concerning pathologic fractures described below were kept (B).

TABLE 2. Dose constraints

Constraints			
Bone	$\alpha/\beta = 1.8 \text{ Gy}$	$\alpha/\beta = 2.8 \text{ Gy}$	
V40 < 64%	V23.4 < 64%	V24.8 < 64%	[18]
Dmean < 37 Gy	Dmean < 22.4	Dmean < 23.6 Gy	[18]
D2 < 59 Gy	D2 < 29.3 Gy	D2 < 31.3 Gy	[18]
Circumferential < 50 Gy	Circumferential < 26.4 Gy	Circumferential < 28.3 Gy	Institutional standard
Soft tissue	$\alpha/\beta = 2.0 \text{ Gy}$		
Circumferential < 40 Gy	Circumferential < 23.7 Gy		Institutional standard

veloped wound healing complications requiring a second surgical intervention. In 4 additional patients, minor wound complications occurred (three times seroma requiring puncture, once protracted wound healing and hematoma). An example of a treatment plan for a thigh sarcoma (the largest tumour in our cohort) shows good feasibility and dose coverage of the target volume while keeping all dose constraints described below (Figure 1).

### Oncologic outcomes

Median follow up for all patients was  $5.1 \pm 1.6$  months. Three tumours were resected with microscopically positive margins. In one patient a wide resection without major functional deficits was not feasible. Therefore, a planned positive margin resection was performed. None of the tumours developed a pathologic remission with < 10% vital tumour cells in the resection specimen. Percentage of vital tumour cells was 50% median with a range of 20–95%. The percentage of vital tumour cells did not correlate with the time from end of radiotherapy to surgery (Pearson correlation coefficient  $r = -0.01$ ). Two patients developed a local recurrence, one patient with simultaneous distant metastases five months after start of treatment, one patient 3 months after start of treatment after having developed distant metastases 2 months after start of therapy. All patients developing local recurrences had positive surgical margins. One patient developed pulmonary metastases 3 months after treatment. One patient developed one new distant sarcoma lesion which was treated curatively (Table 1). Thus, estimated local control and disease free survival at 6 months was  $92 \pm 8\%$  and  $84 \pm 10\%$ , respectively. All tumours which developed local and/or distant recurrence showed poorly differentiated histologies (G3).

### Dose constraints

As the dose constraints used for radiotherapy of extremity sarcomas (especially for bone concerning pathologic fractures and soft tissue concerning lymphedema) have been developed for normofractionated radiotherapy with 1.8–2.0 Gy per fraction, the question arises, what the corresponding dose constraints for hypofractionated radiotherapy with 25.0 Gy in 5 fractions are. In order to get an estimate of equivalent doses, a literature search was performed to find  $\alpha/\beta$  values for bone fracture and soft tissue. For pathologic rib fractures after radiotherapy for breast cancer  $\alpha/\beta$  values between 1.8 Gy and 2.8 Gy were described.<sup>17</sup> To our knowledge,  $\alpha/\beta$  values for soft tissue concerning lymph oedema have not yet been reported, for the calculation we opted for a value of 2.0 Gy (typically assumed for late radiation toxicity). With an estimate of the  $\alpha/\beta$  values, corresponding doses for institutional constraints as well as published constraints for bone fractures in the radiotherapy of soft tissue sarcomas were calculated as shown in Figure 2. Dose per fraction for the constraints for normofractionated radiotherapy was fixed to 2 Gy, although dose per fraction varies with the number of fractions for the same total dose (e.g. 40 Gy circumferential would refer to a dose per fraction of 1.6 Gy for 25 fractions in preoperative radiotherapy or 1.2 Gy for postoperative radiotherapy in 33 fractions).

With our institutional constraint for bone irradiation at extremities, including the whole bone in the irradiated volume, is unproblematic as the corresponding constraint to 50.0 Gy for the whole bone circumference is between 26.4 Gy and 28.3 Gy depending on the assumed  $\alpha/\beta$  value and thus above the prescribed dose. The corresponding dose constraints based on the constraints reported by Dickie *et al.*, are shown in Table 2.<sup>18</sup> With our in-

$$\text{EQD2} = \frac{d + \alpha/\beta}{2 Gy + \alpha/\beta} \times 5d$$

$$\frac{5d^2 + 5\alpha/\beta \times d}{2 Gy + \alpha/\beta} = \text{EQD2}$$

$$5 \times d^2 + 5 \alpha/\beta \times d = \text{EQD2} \times (2 Gy + \alpha/\beta)$$

$$d^2 + \alpha/\beta \times d - \frac{\text{EQD2} \times (2 Gy + \alpha/\beta)}{5} = 0$$

$$d = -\frac{\alpha/\beta}{2} + \sqrt{\frac{(\alpha/\beta)^2}{4} + \frac{\text{EQD2} \times (2 Gy + \alpha/\beta)}{5}}$$

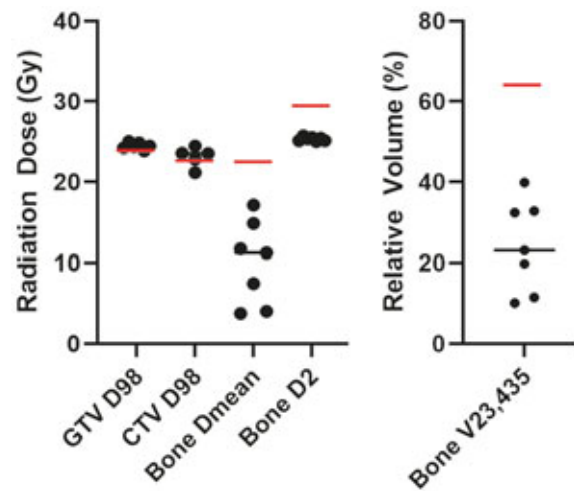
$$\text{constr}_{\text{HFX}} = 5 \times \left( -\frac{\alpha/\beta}{2} + \sqrt{\frac{(\alpha/\beta)^2}{4} + \frac{\text{constr}_{\text{NFX}} \times (2 Gy + \alpha/\beta)}{5}} \right)$$

**FIGURE 2.** Starting from the equation for equivalent dose 2 Gy (EQD2) for a hypofractionated radiation regimen in 5 fractions, the quadratic equation for the single dose in five fractions corresponding to the known EQD2 was derived. Solving the quadratic equation leads to the dose per fraction for five fractions corresponding to the given EQD2 (assuming a known  $\alpha/\beta$  value for tumour control or side effects in OARs, respectively). Dose per fraction for the constraints for normofractionated radiotherapy was fixed to 2 Gy, although dose per fraction varies with the number of fractions for the same total dose (e.g. 40 Gy circumferential dose would refer to a dose per fraction of 1.6 Gy for 25 fractions in preoperative radiotherapy or 1.2 Gy for postoperative radiotherapy in 33 fractions). As dose constraints for normofractionated radiotherapy normally are not corrected for number of fractions in clinical plan evaluation, they were not corrected to EQD2 for the transfer to the hypofractionated regimen.  $\text{constr}_{\text{HFX}}$  = constraint for hypofractionated radiotherapy.  $\text{constr}_{\text{NFX}}$  = constraint for normofractionated radiotherapy.

stitutional standard for the whole circumferential soft tissue to avoid lymphedema of circumferential 40.0 Gy, corresponding dose for 25.0 Gy in 5 fractions is 23.7 Gy (with an assumed  $\alpha/\beta$  value of 2.0 Gy). Thus sparing of at least a part of the circumferential soft tissue is crucial to keep the constraint during hypofractionated radiotherapy with 25.0 Gy in 5 fractions (for details see Table 2).

### Radiotherapy planning results

For seven patients with lower extremity sarcomas dose coverage of the target volume as well as the newly established dose constraints for bone were recorded. GTV coverage was good in all cases. CTV coverage was below the dose aimed for in one of the six patients (large calf sarcoma with a CTV reaching the skin in large areas). All dose constraints described in Table 2 were met in all patients (Figure 3). Circumferential dose constraints



**FIGURE 3.** Radiation planning parameters were evaluated for seven of nine patients with sarcomas of the lower extremity. For bone constraints concerning pathologic fracture the whole femur or the whole tibia were contoured for thigh and calf sarcomas, respectively. Black bars indicate the median values, red bars indicate the assumed constraints as described in Table 2 and in the main text (for bone with  $\alpha/\beta = 1.8$  Gy, worst case scenario). Gross tumour volume (GTV) coverage was reached in all cases. D98 for clinical target volume (CTV) fell short in one patient with a large calf sarcoma with a CTV reaching the skin in large areas. Re-calculated dose constraints for pathologic fracture were not reached in any case.

to the bone and soft tissue circumference were met in all cases (data not shown).

### Discussion

High risk soft tissue sarcomas in geriatric patients pose difficult treatment decisions.<sup>7,19</sup> Standard therapy for these tumours consisting of multimodal therapy over several weeks to months is hardly feasible.<sup>20,21</sup> Surgical approaches are also limited by the functional reserves of patients. Additional radiotherapy significantly reduces the risk of local recurrence.<sup>22</sup> In an analysis of geriatric patients with a lower age than in our group including also low risk tumours (American Joint Committee on Cancer [AJCC] stage I) only 22% received radiotherapy. The recurrence rate was comparable or even higher than in our cohort with 27%.<sup>23</sup> Thus, the strategy of hypofractionated preoperative radiotherapy followed by wide resection of the tumour was adopted for this specific patient population.

With pre-treatment interdisciplinary patient evaluation, feasibility of the multimodal concept was good with 17 of 18 (94%) patients completing treatment (radiotherapy and surgery). One

patient did not undergo surgery after completing radiotherapy which resulted in palliative radiotherapy to reduce symptoms caused by the tumour. Postoperative complication rate is not significantly higher than reported for soft tissue sarcomas in general with 5 of 17 (30%) patients requiring surgical intervention compared to 29 of 122 (24%) in a large retrospective analysis (Chi-square:  $p = 0.17$ ).<sup>24</sup> In a systematic review and metaanalysis, lower rates for re-surgeries of 16% were reported. However, the specific patient population in our study represents a high risk population for wound complication concerning the described risk factors of age, comorbidities and deep-seated high-grade tumours.<sup>25</sup>

Our early oncologic results with a local control rate of 92% and a disease-free survival of 84% after 6 months, respectively, were comparable to published data of 87% and 76%, respectively in a dataset of 188 patients with longer follow up.<sup>26</sup> None of the patients in our analysis developed an isolated local recurrence. Although the reported dataset is limited in number of patients and short follow-up, our data do not hint at an excessive risk for local recurrence taking into account compromised surgical approaches and chemotherapy options in this specific patient cohort.

To our knowledge, this is the first presentation of the transfer of dose constraints for radiotherapy of the extremities (focusing on bone and soft tissue) for the altered fractionation schedule with 25.0 Gy in 5 fractions. To our knowledge, the quantitative analyses of normal tissue effects in the clinic (QUANTEC) publications do not comment on dose constraints for bone concerning pathologic fracture or soft tissue related to lymph edema.<sup>27</sup> We calculated adjusted dose constraints from our institutional constraints for normofractionated radiotherapy as well as from dose constraints published as risk factors for pathologic fractures in sarcoma radiotherapy.<sup>18</sup> Keeping the adjusted institutional constraints was possible in all cases treated in this series without compromising target volume coverage. The constraints listed in the table are a starting point to develop guidance for the altered fractionation in hypofractionated preoperative radiotherapy for extremity soft tissue sarcomas. However, with assumptions to be made such as the  $\alpha/\beta$  value that is hardly known for pathologic fractures or lymph oedema (to our knowledge the only report is on rib fractures after radiotherapy to the thoracic wall), long term side effects of this treatment schedule will need further evaluation.<sup>17</sup>

Another field for further development of dose constraints (even for normofractionated radio-

therapy) would be taking into account the number of fractions and calculating dose constraints with equivalent dose 2 Gy (EQD2) correction. This strategy would allow for better comparison of dose constraints and side effects between different radiotherapy fractionation schedules as reported by Jaikuna *et al.*<sup>28</sup>

## Conclusions

In conclusion, hypofractionated preoperative radiotherapy is a feasible and (at least concerning acute wound complications) safe treatment option for geriatric patients with high risk soft tissue sarcoma after critical interdisciplinary evaluation by the surgeon and anesthesiologist as well as the radiation oncologist. The treatment concept warrants further evaluation in this distinct patient population in order to enable perioperative radiotherapy for high risk soft tissue sarcomas.

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