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Original article

Intraoperative electron radiation therapy combined with external beam radiation therapy and limb sparing surgery in extremity soft tissue sarcoma: a retrospective single center analysis of 183 cases

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ABSTRACT

Background and purpose: To report our experience with limb-sparing surgery, IOERT and EBRT in extremity STS.
Materials and methods: 183 patients were retrospectively analyzed. 78% presented in primary situation, with 80% located in the lower limb. Stage at presentation was: I: 6%, IIa: 25%, IIb: 21%, III: 42%, IV: 7%. The majority showed high-grade lesions (grade 1: 5%, 2: 31%, 3: 64%). IOERT was applied to the tumor bed (median 15 Gy) and preceded (9%) or followed (91%) by EBRT (median 45 Gy) in all patients.
Results: Median follow-up was 64 months (78 months in survivors). Surgery was complete in 68%, while 32% had microscopic residual disease. 5- and 10-year-LC was 86% and 84%, respectively. LC was significantly higher in primary compared to recurrent disease and tended to be higher after complete resection. Estimated 5- and 10-year-DC was 68% and 66%, while corresponding OS was 77% and 66%, respectively. OS was significantly affected by grading and stage. Severe postoperative complications and late toxicities were observed in 19% and 20%, respectively. Limb-preservation rate was 95% with good function in 83%.
Conclusions: Combination of limb-sparing surgery, IOERT and EBRT achieved encouraging LC and OS in this unfavorable patient group with acceptable postoperative complications and low rates of late toxicities resulting in a high limb-preservation rate and good functional outcome.

Soft tissue sarcomas (STS) represent a rare tumor entity, accounting for less than 1% of adult malignancies [1]. The majority is located in the extremities with a predisposition to the lower limb [2]. The cornerstone of curative intent treatment is surgery with negative margins. Since Rosenberg et al. [3] showed similar overall survival comparing amputation with limb sparing surgery followed by radiation therapy (RT), the combination approach has emerged as the standard of care in extremity sarcomas with high risk features. Postoperative RT undoubtedly results in increased rates of local control (LC) [4], but high doses of ⩾60 Gy must be applied to large volumes, which can be associated with marked acute and late toxicities and consequently result in unfavorable functional outcomes [5]. Therefore different strategies have been investigated to reduce toxicities and improve functional outcome without compromising LC especially in patients with close/positive surgical margins. For example, preoperative radiation has been shown to result in lower rates of late toxicities compared to the postoperative approach with similar LC [6,7], which seems to be mainly based on the opportunity to use lower doses and smaller treatment volumes [7]. However, the improvement in late toxicity had to be paid with doubled rates of severe wound complications [6,7]. Another way to reduce the high dose volumes without compromising LC was the introduction of intraoperative radiation therapy (IOERT) or brachytherapy [8,9]. IOERT is a treatment technique, which has been developed for dose escalation

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in body regions, where high doses are hardly achievable with external beam radiotherapy (EBRT) alone because of adjacent organs at risk with much lower tolerance than in extremity regions [10–12]. However IOERT has been introduced by several groups including ours also in the treatment of extremity tumors [2,13–17] to replace the external beam boost mainly because of its unique opportunity to guide a high single dose directly to the high risk region under visual control during surgery. This does not only result in smaller boost volumes because safety margins for daily positioning errors can be omitted, but also in the possibility to exclude organs at risk like major nerves or skin from the radiation field which could at least theoretically reduce late toxicities and improve long term functional outcome [17]. However the results of these series are often difficult to interpret mainly because of small sample sizes, heterogenous patient cohorts (including non-extremity sites, grossly incomplete resections or sarcoma-like histologies), inclusion of different treatment combinations or short follow-up. We therefore report our experience in a large homogenous cohort of patients treated with a combination of limb sparing surgery, IOERT and EBRT and considerable follow-up.

Materials and methods

We conducted a retrospective evaluation of 301 patients with extremity STS who have been treated with IOERT at our institution since 1991. Patients were eligible for the analysis if they suffered from primary or recurrent extremity STS (according to WHO), had received gross total limb-sparing surgery (documented pathological margin) and IOERT at our institution and had received additional (pre- or postoperative) EBRT in conventional fractionation. Patients with metastasectomy prior or during present surgery in curative intent were also eligible. Patients with gross residual disease (R2), missing information about resection margin (R*x*), histology other than STS or tumor localization outside the extremities were excluded. Patients who were treated with IOERT alone, additional EBRT with altered fractionation and patients who received EBRT at another institution without the availability of suitable RT documentation were also excluded. Eligible patients, who had been included in our previous analysis with slightly different inclusion criteria [2] were fully re-evaluated. Patients' charts and reports were reviewed to obtain patient and treatment characteristics. Regular follow-up examinations took place at our institution or at the referring centers. In case of missing follow-up, data were completed by calling the patient or the treating physician. All patients gave written informed consent before treatment. The study is in compliance with the Declaration of Helsinki (Sixth Revision, 2008) and was approved by the Independent Ethics Committee Heidelberg (Ref. Nr. S-164/2012).

A total of 183 patients met the inclusion criteria. Median age was 55 years and median tumor size 8 cm. Most patients presented with primary disease (78%), mainly located in the lower limb (80%). The majority of patients showed high-grade lesions (FNCLCC grade 2/3: 95%), predominantly malignant fibrous histiocytoma/undifferentiated pleomorphic sarcoma (30%) and liposarcomas (28%) in advanced stages (IIb–IV: 70%), see Table 1.

Surgery was performed as wide excision (90%) or compartmental resection (10%) according to sarcoma surgery principles by experienced surgeons. All patients received an IOERT boost to the tumor bed. The technique of IOERT used at our institution was previously published in detail [10–12,16,17]. Briefly, IOERT was performed in a dedicated operation room with an integrated linear accelerator capable of delivering 6–18 MeV electrons. The target area was defined in correspondence with the surgeon and usually included the high risk area for positive margins with a safety margin of 1 cm. Uninvolved radiosensitive tissues (for example major nerves) were displaced or protected by lead shields whenever possible. The median IOERT dose was 15 Gy (range 8–20 Gy), prescribed to the 90%-isodose. IOERT dose was usually restricted to 10–12 Gy, if major nerves had to be included into the radiation field, see Table 1.

Table 1
Patient and Treatment characteristics.

	n	%		*n*	%
Age [yrs]			*Size [cm]*		
Median	55		Median	8	
Range	3–89		Range	1–25	
Gender			*Status*		
Male	112	61	Primary	142	78
Female	71	39	Recurrent	41	22
Localization			*Surgery*		
Upper extremity	37	20	Wide excision	165	90
Lower extremity	146	80	Compartment	18	10
UICC stage (7th ed.)			*Subtype*		
Ia	3	2	Liposarcoma	53	29
Ib	7	4	MFH/UPS	52	28
IIa	46	25	Synovial Sarcoma	28	15
IIb	38	21	Leiomyosarcoma	12	7
III	76	42	Other	38	21
IV	13	7			
Resection margin			*Grading (FNCLCC)*		
R0	125	68	G1	10	5
R1	58	32	G2	56	31
			G3	117	64
EBRT			*CHT*		
Preop	16	9	Yes	71	39
Postop	167	91	No	112	61
EBRT dose [Gy]			*IOERT dose [Gy]*		
Median	45		Median	15	
Range	20–60		Range	8–20	
IOERT Energy [MeV]			*IOERT cone [cm]*		
Median	6		Median	9	
Range	6–12		Range	5–22[a]	

n: Number of patients, %: percentage, yrs: years, UICC: union international contre le cancer, ed.: edition, EBRT: external beam radiation therapy, Gy: Gray, IOERT: intraoperative electron radiation therapy, MeV: mega electron volts, cm: centimeter, MFH: malignant fibrous histiocytoma, UPS: undifferentiated pleomorphic sarcoma, FNCLCC: Federation Nationales des Centres de Lutte Contre le Cancer, CHT: chemotherapy.

[a] Two abutted fields used in some patients.

All patients received additional EBRT pre- (9%) or postoperatively (91%). Usually the PTV included the GTV (preoperatively) or the surgical cavity (postoperatively) with a safety margin of 4–5 cm in longitudinal and 2–3 cm in axial direction. Margins were reduced at uninvolved anatomical borders. The biopsy region or surgical scars were included into the PTV if treated postoperatively. 3D-conformal treatment was routinely performed since 1995. EBRT was applied in conventional fractionation (1.8–2 Gy) with a median dose of 45 Gy (range 20–60 Gy). 90% of the patients received doses of 40–50.4 Gy.

Neoadjuvant and/or adjuvant chemotherapy was not routinely used, however 39% of the patients received either pre- or postoperative chemotherapy or both at the discretion of the treating medical oncologist.

Local control (LC), distant control (DC), freedom from treatment failure (FFTF) and overall survival (OS) were calculated from the date of surgery. LC was defined as absence of tumor regrowth inside the EBRT area or at its margins. In patients without further assessment of LC e.g. after development of distant spread, the date of the last information about the local status was used for calculation. DC was defined as absence of distant spread including

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