Radiotherapy and Oncology 119 (2016) 22–29

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Soft tissue sarcoma

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

Falk Roeder [a,b,c,d,1,*], Burkhard Lehner [e], Ladan Saleh-Ebrahimi [b,d,1], Frank W. Hensley [c,1], Alexis Ulrich [f], Ingo Alldinger [f], Gunhild Mechtersheimer [g], Peter E. Huber [a,c], Robert Krempien [a,h,1], Marc Bischof [a,i,1], Juergen Debus [a,b], Matthias Uhl [a]

[a] *Department of Radiation Oncology, University of Heidelberg;* [b] *CCU Radiation Oncology;* [c] *CCU Molecular Radiation Oncology, German Cancer Research Center (DKFZ), Heidelberg;* [d] *Department of Radiation Oncology, University of Munich (LMU);* [e] *Department of Orthopedics;* [f] *Department of Surgery;* [g] *Institute of Pathology, University of Heidelberg;* [h] *Department of Radiation Oncology, Helios Clinic Berlin-Buch; and* [i] *Department of Radiation Oncology, SLK Clinic Heilbronn, Germany*

ARTICLE INFO

Article history:
Received 4 August 2015
Received in revised form 10 November 2015
Accepted 18 November 2015
Available online 1 December 2015

Keywords:
Extremity
Soft tissue sarcoma
IOERT
EBRT
Limb-sparing surgery

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

* Corresponding author at: Department of Radiation Oncology, University of Munich (LMU), Marchioninistr. 15, 81377 Munich, Germany.

E-mail addresses: Falk.Roeder@med.uni-muenchen.de (F. Roeder), Burkhard.Lehner@med.uni-heidelberg.de (B. Lehner), Ladan.SalehEbrahimi@med.uni-muenchen.de (L. Saleh-Ebrahimi), Frank.Hensley@med.uni-heidelberg.de (F.W. Hensley), Alexis.Ulrich@med.uni-heidelberg.de (A. Ulrich), Ingo.Alldinger@med.uni-heidelberg.de (I. Alldinger), Gunhild.Mechtersheimer@med.uni-heidelberg.de (G. Mechtersheimer), p.huber@dkfz.de (P.E. Huber), Robert.krempien@helios-kliniken.de (R. Krempien), Marc.Bischof@slk-kliniken.de (M. Bischof), Juergen.Debus@med.uni-heidelberg.de (J. Debus), Matthias.Uhl@med.uni-heidelberg.de (M. Uhl).

[1] Addresses 'a (F. Roeder, R. Krempien, M. Bischof)', 'b (F. Roeder, L. Saleh-Ebrahimi)' and 'c (F.W. Hensley)' are former departments of respective authors.

http://dx.doi.org/10.1016/j.radonc.2015.11.014
0167-8140/

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

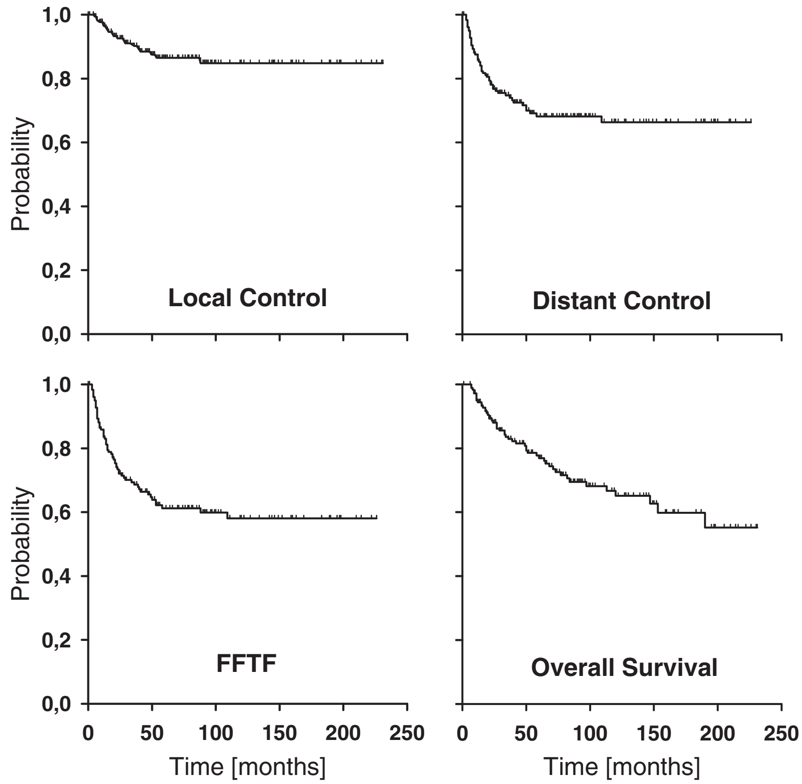

Fig. 1. Outcome (entire cohort). Upper left: LC, upper right: DC, lower left: FFTF, lower right: OS.

non-regional nodal failures. FFTF was defined as absence of local or distant failure. Time to event data was calculated using the Kaplan–Meier method. Differences in subgroups were tested for statistical significance by the log-rank test. Parameters with $p < 0.1$ in univariate analysis were entered into a Cox regression model for multivariate analysis. Differences were considered statistically significant for a p-value of $\leqslant 0.05$. Postoperative complications were reported if they required prolonged hospitalization, readmission or invasive intervention. Acute and late radiation side effects were graded according to CTCAE3.0. Only severe (grade 3 or higher) complications are reported because of the retrospective nature of the analysis to prevent underreporting of lower grade toxicities.

Results

The median follow-up for the entire cohort was 64 months (6–231 months) and 78 months in surviving patients. Surgery resulted in free margins in 125 patients (68%), while 58 patients (32%) showed microscopically positive margins.

The estimated 5- and 10-year-LC rates for the entire cohort were 86% and 84%, respectively (Fig. 1). Median time to onset of a local recurrence was 20 months (5–88 months). LC was significantly associated with resection margin, primary vs recurrent situation and grading in univariate analysis (Table 2, Fig. 2). On multivariate analysis, only disease situation (primary/recurrent) remained statistically significant, although a clear trend was present also for resection margin ($p = 0.057$).

The estimated 5- and 10-year-DC rates for the entire cohort were 68% and 66%, respectively (Fig. 1). Median time to onset of a distant failure was 14 months (3–109 months) and the lung (46%) was most frequently affected. DC was significantly influenced by tumor size, grading, metastases prior/at IOERT and stage in univariate analysis (Table 2, Figs. 2 and 3). A trend was also seen for histology, with liposarcomas showing the best (80%) and leiomyosarcomas the worst (42%) 5-year-DC rates (Table 2). On multivariate analysis, histology, size and metastases prior/at IOERT were significantly associated with DC, while only a trend was observed for grading.

The estimated 5- and 10 year-FFTF rates were 61% and 58%, respectively (Fig. 1). Of the observed failures, 20% were isolated local recurrences, 69% were isolated distant metastases and 11% were combined failures. FFTF was significantly associated with primary vs recurrent situation, grading, metastases prior/at IOERT and stage in univariate analysis (Table 2, Fig. 3). Trends were also seen for resection margin and histology, with liposarcomas showing the best (73%) and leiomyosarcomas the worst (31%) 5-year-FFTF rates. On multivariate analysis, disease situation (primary/recurrent), grading and metastases prior/at IOERT remained statistically significant.

The estimated 5- and 10 year-OS rates were 77% and 66%, respectively (Fig. 1). OS was significantly associated with grading, metastases prior/at IOERT and stage in univariate analysis (Table 2, Figs. 2 and Fig. 3). A trend was observed for resection margin. On multivariate analysis, only grading and metastases at/prior to IOERT remained statistically significant.

Postoperative complications were documented in 34 patients (19%), mainly wound healing disturbances, local infections, abscess/fistula formation or hematoma, see Table 3. Severe radiation-related acute side effects were very rare (1%), including one patient with grade3 dermatitis and one with abscess formation. Late side effects were scored in 37 patients (20%), including neuropathy in 14 patients (8%) and radionecrosis/fractures in 11 patients (6%), see Table 3. Secondary amputations were needed in 9 patients (6 recurrence, 1 infection, 1 bypass dysfunction), transferring into a final limb preservation rate of 95%. Preserved limb function without impairment of activities of daily living was observed in 145 of the remaining 174 patients (83%).

Table 2
Univariate analysis (LC, DC, FFTF, OS).

Univariate analysis	LC		DC		FFTF		OS	
	5-yr (%)	*p*	5-yr (%)	*p*	5-yr (%)	*p*	5-yr (%)	*p*
Gender								
Male	86	0.629	69	0.613	63	0.581	76	0.827
Female	87		67		59		78	
Age								
<55 yrs	91	0.111	71	0.817	69	0.214	80	0.177
⩾55 yrs	82		66		55		75	
Situation								
Primary	90	**0.008**	70	0.232	66	**0.002**	78	0.441
Recurrent	74		62		44		74	
Localization								
Upper limb	80	0.238	71	0.533	55	0.591	76	0.851
Lower limb	88		67		63		82	
Histology								
Liposarcoma	85	0.192	80	0.098	71	0.082	87	0.284
Leiomyosarcoma	80		42		33		55	
MFH/UPS	85		69		61		74	
Synovial sarcoma	100		68		68		80	
Other	80		60		52		74	
Grading								
G1	80	**0.043**	90	**0.001**	70	**0.007**	100	**0.001**
G2	95		81		78		89	
G3	82		60		52		69	
Size								
⩽5 cm	81	0.348	83	**0.033**	70	0.225	81	0.333
>5 cm	89		62		58		75	
Met prior/at IOERT								
No	87	0.285	72	**0.001**	65	**0.001**	80	**0.001**
Yes	80		14		13		43	
UICC (7th)								
Stage 1	80	0.292	90	**0.001**	70	**0.001**	100	**0.001**
Stage 2	88		81		74		87	
Stage 3	87		58		53		71	
Stage 4	80		14		14		38	
Type of surgery								
Wide	86	0.807	68	0.651	61	0.494	78	0.726
Compartimental	87		71		65		77	
Resection margin								
R0	92	**0.019**	70	0.592	68	0.072	80	0.195
R1	75		64		49		71	
RT timing								
Preoperative	85	0.981	68	0.969	56	0.755	81	0.298
Postoperative	87		68		62		76	
CHT								
No	84	0.305	72	0.112	60	0.851	80	0.339
Yes	91		63		64		73	

LC: local control, DC: distant control, FFTF: freedom from treatment failure, OS: overall survival, 5-yr: 5-year rate, yrs: years, MFH: malignant fibrous histiocytoma, UPS: undifferentiated pleomorphic sarcoma, cm: centimeter, met: metastases, IOERT: intraoperative electron radiation therapy, UICC: Union international contre le cancer, CHT: chemotherapy, bold: significant *p*-values.

Discussion

Here we report the largest series of patients with extremity STS treated with a combination of limb-sparing surgery, IOERT and EBRT. Using this approach, we observed encouraging results in terms of LC (5-year-rate 86%), DC (68%) and OS (77%) with acceptable postoperative complications and limited late toxicity transferring into high rates of limb preservation (95%) with good functional outcome in the majority of patients (83%).

Our results are in line with other major retrospective series using similar combinations of intraoperative and external beam RT [2,13–15,17–19] (see Table 4), which reported consistently 5-year-LC rates of 80–90%, although their patient cohorts were smaller and less homogenous. Further on, LC seems to be comparable with recent series using EBRT alone (pre- or postoperatively) which reported consistently 5-year-LC rates of 83–93% [20–30] although they usually included far less patients with microscopic residual disease (0–25% vs 33%) and recurrent disease (0–16% vs 22%) compared to our cohort. Both factors have been shown to significantly influence LC in our and other major series. For example Zagars et al. [20] similarly reported significant differences in 5-year-LC according to margin status (88% vs 64%) and disease situation (85% vs 70%) in 1225 patients treated with surgery and EBRT. Unfortunately, many other recent series do not report 5-year-LC results separated according to R0 vs R1 or primary vs recurrent situation making direct comparisons difficult. Dagan et al. [22] found a lower 5-year-LC rate of 69% after R1 resection and O'Sullivan et al. [31] even described only 50% with EBRT alone. On the other hand, Felderhof et al. [25] found a crude LC rate of 86% in R1 resected patients with postoperative EBRT. Al Yami et al. [32]

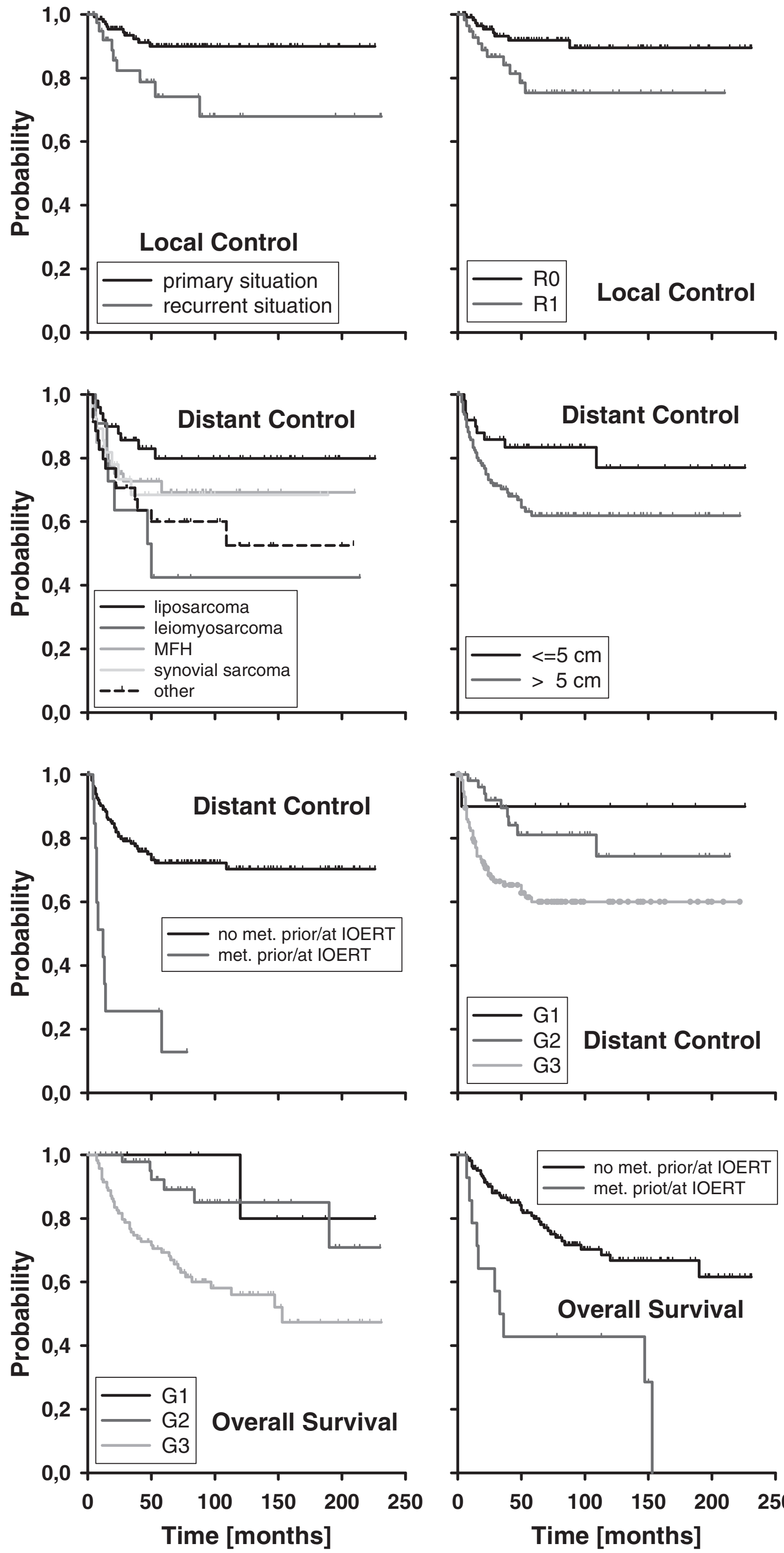

Fig. 2. Prognostic factors. First row: regarding LC, second/third row: regarding DC, last row: regarding OS.

described an overall crude LC rate of 84% after R1 resection with preoperative EBRT with or without a postoperative boost, although they observed a 5-year-LC rate of 90% vs 74% in favor of the group not receiving a boost indicating a high probability of an inherent selection bias in their analysis. Given similar overall LC rates in series with IOERT compared to the EBRT alone and keeping in mind the inclusion of far more unfavorable patients into the IOERT series in terms of resection margin and disease situation, one might argue that IOERT can compensate the negative impact of those unfavorable features at least in some patients. This might be due to the increased biological effect of a high single dose guided directly under visual control to the high risk region. However, given the

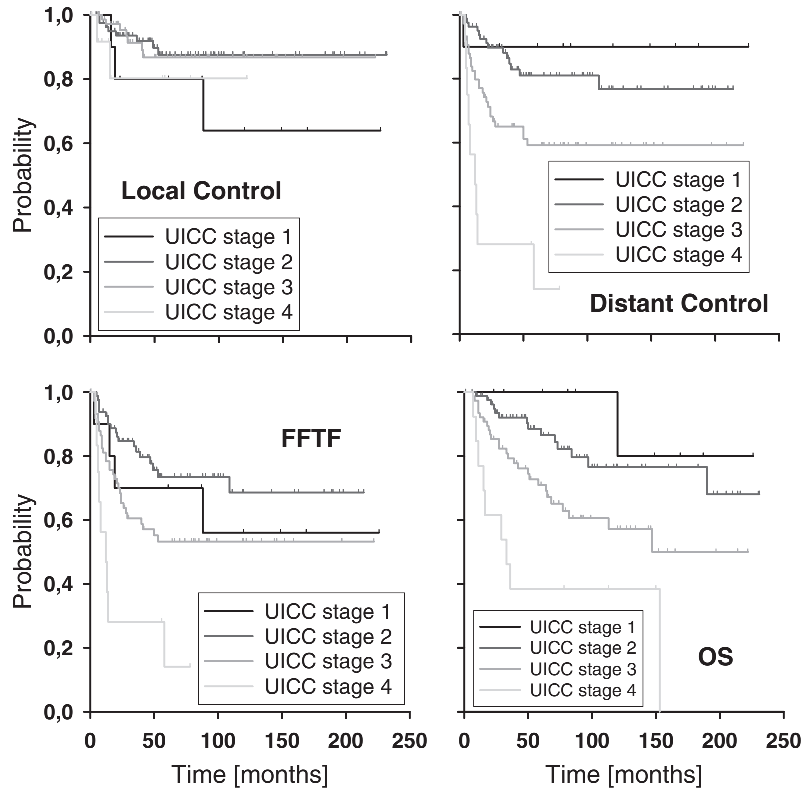

Fig. 3. Outcome according to stage (UICC (7th)). Upper left: LC, upper right: DC, lower left: FFTF, lower right: OS.

Table 3
Postoperative complications and late toxicities.

	n	%
Postoperative complication		
Wound healing disturbance	15	8
Infection/abscess/fistula	9	4
Hematoma	7	4
Necrosis	3	2
Lymph fistula	3	2
Bleeding	2	1
Thrombosis	2	1
PAOD	1	1
Sepsis	1	1
Myocardial infarction	1	1
Apoplex	1	1
Acute renal failure	1	1
Pulmonary embolism	1	1
Severe late toxicity		
Neuropathy[a]	14	8
Osteonecrosis/fracture/pseudoarthrosis	11	6
Contracture/fibrosis/joint stiffness	6	3
Lymphedema	6	3
Arterial stenosis	4	2
Erysipelas	1	1
Prothetic implant infection	1	1
Prothetic implant fracture	1	1
Ulceration	1	1

PAOD: peripheral arterial occlusive disease, *n*: number of patients, %: percentage.
Some patients had more than one complication.
Some patients had more than one severe late toxicity.
[a] 7 patients with nerve resections included.

retrospective nature of most of the series, the known difficulties in comparing different series in general and the wide range of results reported for the mentioned subgroups, it cannot be ruled out that this effect occurs by selection bias or randomly. Further on our data clearly show, that IOERT cannot fully compensate an unfavorable surgical outcome (R1 resection) or disease biology (recurrent situation) per se. In this context, the use of particle treatment might be of further interest. Particle beams like protons or heavy ions have recently shown very high local control rates in so-called "radioresistant" tumor entities [33–37] even if gross residual disease was present. Recent data from large single center series showed very encouraging results for chondrosarcoma and chordoma [38,39]. For extremity soft-tissue sarcoma mainly dosimetric comparisons have been published [40] so far, showing small benefits compared to modern photon techniques, while clinical data are scarce. Nevertheless, particles might be an interesting opportunity especially in incompletely resected patients and should be further investigated in terms of efficacy and toxicity.

Regarding other endpoints like DC, FFTF and OS, we observed similar results compared to other series with or without IOERT [13,19,20,41]. As described by many other reports [20,41], the most important prognostic factors for disease control were grading and stage at presentation. Unsurprisingly, patients with metastases prior/at IOERT did worse in all non-local endpoints, however even those achieved a 5-year-OS rate of 43% indicating the opportunity for long term survival in a substantial proportion of stage IV patients if properly selected and adequately treated. Although not statistically significant on multivariate analysis, we further observed distinct differences in outcome according to histology with liposarcomas doing the best and leiomyosarcomas doing the worst, indicating that the latter ones might benefit from intensified systemic therapy as suggested by others [20].

Aside from LC, there is an ongoing debate not only about the value of additional boosting techniques like IOERT, but also about the timing of EBRT, which is driven mainly by functional issues. Consecutive reports from the prospective randomized NCIC trial comparing preoperative and postoperative EBRT failed to show significant differences in oncological outcome, but reported marked differences in wound complications and severe late toxicities

Table 4
Results of major IORT series.

Author	Year	*n*	f/u	R0 (%)	IORT^m	EBRT^m	5-y-LC	5-y-OS	LP (%)	FC (%)
Edmonson [13]	2001	39	70	62	10–20	45	90[a]	80	95	n.r.
Azinovic [14]	2003	45	93	67	15	45–50	80[a]	64[a]	88	77
Kretzler [15]	2004	28	52	61	12–15	50	84	66	100	59
Llacer [18]	2006	79	58	42	20 (LDR)	45–50	90	69	100	n.r.
Oertel [2]	2006	128[b]	33	49	15	45	83	83	90	86
Alvarez [19]	2008	53	66	n.r.	7.5–12.5	n.r.	87	75	83	81
Roeder [17]	2013	34	43	88	10–15	40–50	97	79	94	81
Current study	2015	183	64	68	15	45	86	71	95	83

n: number of patients, f/u: median follow up, %: percentage, R0: rate of microscopic complete resections, IORT: intraoperative radiation therapy dose in Gy, LDR: low dose rate brachytherapy, EBRT: external beam radiation therapy dose in Gy, ^{m}: median doses (if specified), 5-y-LC: estimated 5-year-local control rate in %, 5-y-OS: estimated 5-year-overall survival rate in %, LP: limb preservation rate, FC (%): rate of excellent/good functional outcome,
[a] Crude rates.
[b] Excluding patients with distant metastases at time of surgery.

(fibrosis, edema, joint stiffness) favoring the postoperative arm regarding the former and the preoperative arm regarding the latter issues [6,7,42]. Although functional outcome analysis revealed no significant differences between the treatment arms, severe fibrosis, edema and joint stiffness were associated with lower functionality scores in general and their onset increased with field size [7]. Stinson et al. [5] also reported associations between increased total dose and/or field size with late toxicities in postoperatively irradiated patients. Recently, Alektiar et al. [43] and ÓSullivan et al. [31] found low rates of late toxicities with the use of IMRT in the post- and preoperative setting. Dickie et al. [44] and Wang et al. [45] further described low rates of late toxicities using image-guided approaches. In summary those studies suggest a clear relationship between the high-dose irradiated volume and the onset of severe late effects.

Compared to postoperative EBRT alone, introduction of an IOERT boost instead of the percutaneous boost should also lead to a reduction in field size at least regarding the high-dose areas, which may consequently result in reduced late toxicity and improved functional outcome [17]. In contrast to preoperative EBRT, a markedly increased wound complication rate compared to postoperative EBRT alone seems unlikely, because the skin is excluded from the boost area [17]. Further on, the postoperative percutaneous dose can be reduced moderately. These assumptions are, at least in part, supported by our results.

We observed a postoperative complication rate of 19%, which is similar to series using postoperative EBRT alone [6] and compares favorably with series using preoperative EBRT [6,21] underlining that the use of an IOERT boost does not increase the wound complication rate [46]. Moreover, the rate of acute radiation-related side effects was very low and compares favorably with series using postoperative EBRT alone [25], which is probably related to the reduced EBRT doses, at least by omitting the external boost.

The overall rate of severe late toxicity found in our study was in the range of other series (3% to >22%) reporting on patients treated with surgery and radiation for extremity sarcomas without IOERT [5,25]. We observed rather low rates of fibrosis, lymph edema and joint stiffness compared to other reports. For example, Davis et al. [7] described fibrosis grade ⩾2 in 48%, joint stiffness in 23% and edema in 23% of the patients treated with postoperative EBRT and Alektiar et al. [43] found 19% grade 2 joint stiffness and 13% edema even using IMRT. O'Sullivan et al. [31] described moderate fibrosis in 9%, edema in 11% and joint stiffness in 6% using preoperative IG-IMRT. Of course, late toxicity might be underreported due to the retrospective nature of our analysis, thus biasing any comparison. However this kind of bias is usually more pronounced in less severe grades of toxicities with little impact on clinical decision making. Interestingly, we found very similar rates of severe toxicities in a recent subgroup analysis of a prospective trial conducted by our group, which evaluated the value of the same combination approach augmented by preoperative and postoperative chemotherapy, indicating the absence of a large bias at least in regard to severe toxicities [17]. Nevertheless, we found considerable rates of bone necrosis/fractures and severe neuropathy, which have been described as dose limiting side effects for IOERT in other parts of the body [47]. In our analysis, 11 patients (6%) developed bone necrosis and/or fracture, which is in the range of reported rate (1–8%) with [14,46] or without IOERT [43,48,49] as part of radiation therapy. The same rate (6%) has been reported using IMRT alone [43]. Considering neuropathy, we observed 14 cases in total (8%) of whom 7 (4%) were attributable to radiation while the others had surgical nerve resections. Again, similar rates have been reported using EBRT alone [43,50]. Unfortunately inclusion/exclusion of major nerves into the IOERT field was not routinely documented in our series. However, the already mentioned subgroup analysis of a prospective trial conducted by our group revealed a severe neuropathy rate of 8% in patients with inclusion of major nerves into the IOERT field [17], which is similar to the findings of Azinovic et al. [14] using also a combination of IOERT and EBRT, thus indicating that major nerves should be excluded from IOERT fields whenever possible.

In summary, the combination of limb-sparing surgery, IOERT and EBRT with moderate doses resulted in encouraging local control and overall survival in this unfavorable patient cohort. Introduction of an IOERT boost did not increase the postoperative complication rate. The combination of IOERT and EBRT yielded very low rates of acute radiation-related side effects and resulted in low rates of late toxicities with a high limb-preservation rate and good functional outcome. Combination of an IOERT boost with modern EBRT techniques like IGRT and IMRT could result in further improved functional outcome and should be tested in prospective trials.

Conflict of interest statement

All authors declare no conflicts of interest.

References

[1] Jemal A, Siegel R, Ward E, Hao Y, Xu J, Thun MJ. Cancer statistics 2009. CA Cancer J Clin 2009;59:225–49.
[2] Oertel S, Treiber M, Zahlten-Hinguranage A, et al. Intraoperative electron boost radiation followed by moderate doses of external beam radiotherapy in limb-sparing treatment of patients with extremity soft-tissue sarcoma. Int J Radiat Oncol Biol Phys 2006;64:1416–23.
[3] Rosenberg SA, Tepper J, Glatstein E, et al. The treatment of soft-tissue sarcomas of the extremities. Ann Surg 1982;196:305–14.
[4] Jebsen NL, Trovik CS, Bauer HC, et al. Radiotherapy to improve local control regardless of surgical margin and malignancy grade in extremity and trunk wall soft tissue sarcoma: a Scandinavian sarcoma group study. Int J Radiat Oncol Biol Phys 2008;71:1196–203.

[5] Stinson SF, DeLaney TF, Greenberg J, et al. Acute and long-term effects on limb function of combined modality limb sparing therapy for extremity soft tissue sarcoma. Int J Radiat Oncol Biol Phys 1991;21:1493–9.
[6] ÓSullivan B, Davis AM, Turcotte R, et al. Preoperative versus postoperative radiotherapy in soft-tissue sarcoma of the limbs: a randomized trial. Lancet 2002;359:2235–41.
[7] Davis AM, ÓSullivan B, Turcotte R, et al. Late radiation morbidity following randomization to preoperative versus postoperative radiotherapy in extremity soft tissue sarcoma. Radiother Oncol 2005;75:48–53.
[8] Eble MJ, Lehnert T, Schwarzbach M, Ewerbeck V, Herfarth C, Wannenmacher M. IORT for extremity sarcomas. Front Radiat Ther Oncol 1997;31:146–50.
[9] Pisters PW, Harrison LB, Leung DH, Woodruff JM, Casper ES, Brennan MF. Long-term results of a prospective randomized trial of adjuvant brachytherapy in soft tissue sarcoma. J Clin Oncol 1996;14:859–68.
[10] Roeder F, Ulrich A, Habl G, et al. Clinical phase I/II trial to investigate preoperative dose-escalated intensity-modulated radiation therapy (IMRT) and intraoperative radiation therapy (IORT) in patients with retroperitoneal soft tissue sarcoma: interim analysis. BMC Cancer 2014;14:617.
[11] Roeder F, Timke C, Uhl M, et al. Aggressive local treatment containing intraoperative radiation therapy (IORT) for patients with isolated local recurrences of pancreatic cancer: a retrospective analysis. BMC Cancer 2012; 12:295.
[12] Roeder F, Goetz JM, Habl G, et al. Intraoperative electron radiation therapy (IOERT) in the management of locally recurrent rectal cancer. BMC Cancer 2012;12:592.
[13] Edmonson JH, Petersen IA, Shives TC, et al. Chemotherapy, irradiation, and surgery for function-preserving therapy of primary extremity soft-tissue sarcomas. Cancer 2002;94:786–92.
[14] Azinovic I, Martinez Monge R, Javier Aristu J, et al. Intraoperative radiotherapy electron boost followed by moderate doses of external beam radiotherapy in resected soft-tissue sarcomas of the extremities. Radiother Oncol 2003;67: 331–7.
[15] Kretzler A, Molls M, Gradinger R, Lukas P, Steinau HU, Würschmidt F. Intraoperative radiotherapy of soft tissue sarcomas of the extremity. Strahlenther Onkol 2004;180:365–70.
[16] Roeder F, Timke C, Oertel S, et al. Intraoperative electron radiotherapy for the management of aggressive fibromatosis. Int J Radiat Oncol Biol Phys 2010;76:1154–60.
[17] Roeder F, Lehner B, Schmitt T, et al. Excellent local control with IOERT and postoperative EBRT in high grade extremity sarcoma: results from a subgroup analysis of a prospective trial. BMC Cancer 2014;14:350.
[18] Llacer C, Delannes M, Minsat M, et al. Low-dose intraoperative brachytherapy in soft tissue sarcomas involving neurovascular structure. Radiother Oncol 2006;78:10–6.
[19] Alvarez A, Calvo FA, Gonzales C, et al. IORT in soft tissue sarcomas involving extremities: toxicities and long-term functional results [abstract]. Revisiones en cancer 2008;22:s55.
[20] Zagars GK, Ballo MT, Pisters PW, et al. Prognostic factors for patients with localized soft-tissue sarcomas treated with conservation surgery and radiation therapy: an analysis of 1225 patients. Cancer 2003;97:2530–43.
[21] Hui AC, Ngan SY, Wong K, Powell G, Choong PF. Preoperative radiotherapy for soft tissue sarcoma: the Peter MacCallum Cancer Centre Experience. Eur J Surg Oncol 2006;32:1159–64.
[22] Dagan R, Indelicato DJ, McGee L, et al. The significance of a marginal excision after preoperative radiation therapy of soft tissue sarcoma of the extremity. Cancer 2012;118:3199–207.
[23] MacDermed DM, Miller LL, Peabody TD, et al. Primary tumor necrosis predicts distant control in locally advanced soft tissue sarcomas after preoperative concurrent chemoradiotherapy. Int J Radiat Oncol Biol Phys 2010;76:1147–53.
[24] Kraybill WG, Harris J, Spiro IJ, et al. Phase II Study of neoadjuvant chemotherapy and radiation therapy in the management of high-risk, high-grade, soft tissue sarcomas of the extremities and body wall: radiation therapy oncology group trial 9514. J Clin Oncol 2006;24:619–25.
[25] Felderhof JM, Creutzberg CL, Putter H, et al. Long term clinical outcome of patients with soft-tissue sarcomas treated with limb-sparing surgery and postoperative radiotherapy. Acta Oncol 2012;52:745–52.
[26] Alektiar KM, Brennan MF, Singer S. Local Control comparison of adjuvant brachytherapy to intensity-modulated radiotherapy in primary high-grade sarcoma of the extremity. Cancer 2011;117:3229–34.
[27] Lee J, Park YJ, Yang DS, et al. Treatment outcome of conservative surgery plus postoperative radiotherapy for extremity soft tissue sarcoma. Radiat Oncol J 2012;30:62–9.
[28] Sampath S, Schultheiss TE, Hitchcock YJ, Randall RL, Shrieve DC, Wong JY. Preoperative versus postoperative radiotherapy in soft-tissue sarcoma: multi-institutional analysis of 821 patients. Int J Radiat Oncol Biol Phys 2011;81:498–505.
[29] Folkert M, Singer S, Brennan MF, et al. Comparison of local recurrence with conventional and intensity-modulated radiation therapy for primary soft-tissue sarcomas of the extremity. J Clin Oncol 2014;32:3236–41.
[30] Rosenberg LA, Esther RJ, Erfanian K, et al. Wound complications in preoperatively irradiated soft-tissue sarcomas of the extremities. Int J Radiat Oncol Biol Phys 2013;85:432–7.
[31] O'Sullivan B, Griffin AM, Dickie CL, et al. Phase 2 study of preoperative image-guided intensity-modulated radiation therapy to reduce wound and combined modality morbidities in lower extremity soft-tissue sarcoma. Cancer 2013;119:1878–94.
[32] Al Yami A, Griffin AM, Ferguson PC, et al. Positive surgical margins in soft tissue sarcoma treated with preoperative radiation: is a postoperative boost necessary? Int J Radiat Oncol Biol Phys 2010;4:1191–7.
[33] Jensen AD, Poulakis M, Nikoghosyan AV, et al. High-LET radiotherapy for adenoid cystic carcinoma of the head and neck: 15 years' experience with raster-scanned carbon ion therapy. Radiother Oncol 2015 [Epub ahead of print].
[34] Jensen AD, Poulakis M, Nikoghosyan AV, et al. Re-irradiation of adenoid cystic carcinoma: analysis and evaluation of outcome in 52 consecutive patients treated with raster-scanned carbon ion therapy. Radiother Oncol 2015;114: 182–8.
[35] Qi WX, Fu S, Zhang Q, et al. Charged particle therapy versus photon therapy for patients with hepatocellular carcinoma: a systematic review and meta-analysis. Radiother Oncol 2015;114:289–95.
[36] Takagi M, Demizu Y, Hashimoto N, et al. Treatment outcomes of particle radiotherapy using protons or carbon ions as a single-modality therapy for adenoid cystic carcinoma of the head and neck. Radiother Oncol 2014;113: 364–70.
[37] Koto M, Hasegawa A, Takagi R, et al. Feasibility of carbon ion radiotherapy for locally advanced sinonasal adenocarcinoma. Radiother Oncol 2014;113: 60–5.
[38] Uhl M, Mattke M, Welzel T, et al. High control rate in patients with chondrosarcoma of the skull base after carbon ion therapy: first report of long-term results. Cancer 2014;120:1579–85.
[39] Uhl M, Mattke M, Welzel T, et al. Highly effective treatment of skull base chordoma with carbon ion irradiation using a raster scan technique in 155 patients: first long-term results. Cancer 2014;120:3410–7.
[40] Fogliata A, Scorsetti M, Navarria P, et al. Dosimetric comparison between VMAT with different dose calculation algorithms and protons for soft-tissue sarcoma radiotherapy. Acta Oncol 2013;52:545–52.
[41] Weitz J, Antonescu CR, Brennan MF. Localized extremity soft tissue sarcoma: improved knowledge with unchanged survival over time. J Clin Oncol 2003; 21:2719–25.
[42] ÓSullivan B, Davis AM, Turcotte R, et al. Five-year results of a randomized phase III trial of pre-operative vs post-operative radiotherapy in extremity soft-tissue sarcoma [abstract]. J Clin Oncol 2004;22:s819.
[43] Alektiar KM, Hong L, Brennan MF, Della-Biancia C, Singer S. Intensity modulated radiation therapy for primary soft tissue sarcoma of the extremity: preliminary results. Int J Radiat Oncol Biol Phys 2007;68:458–64.
[44] Dickie CI, Parent AL, Chung PW, et al. Measuring interfractional and intrafractional motion with cone beam computed tomography and an optical localization system for lower extremity soft tissue sarcoma patients treated with intensity-modulated radiation therapy. Int J Radiat Oncol Biol Phys 2010;78:1437–44.
[45] Wang D, Zhang Q, Eisenberg BL, et al. Significant reduction of late toxicities in patients with extremity sarcoma treated with image-guided radiation therapy to a reduced target volume: results of a radiation therapy oncology group RTOG-0630 trial. J Clin Oncol 2015;33:2231–8.
[46] Kunos C, Colussi V, Getty P, Kinsella T. Intraoperative electron radiotherapy for extremity sarcomas does not increase acute or late morbidity. Clin Orthop Rel Res 2005;446:247–52.
[47] Sindelar WF, Kinsella TJ. Normal tissue tolerance to intraoperative radiotherapy. Surg Oncol Clin N Am 2003;12:925–42.
[48] Cannon CP, Ballo MT, Zagars GK, et al. Complications of combined modality treatment of primary lower extremity soft-tissue sarcomas. Cancer 2006;107:2455–61.
[49] Gortzak Y, Lockwood GA, Mahendra A, et al. Prediction of pathologic fracture risk of the femur after combined modality treatment of soft tissue sarcoma of the thigh. Cancer 2010;116:1553–9.
[50] Rimner A, Brennan MF, Zhang Z, Singer S, Alektiar KM. Influence of compartmental involvement on the patterns of morbidity in soft tissue sarcoma of the thigh. Cancer 2009;115:149–57.