Intraoperative Radiotherapy of Soft Tissue Sarcoma of the Extremity

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Purpose: Evaluation of treatment outcome after intraoperative radiotherapy (IORT) ± external-beam irradiation (EBRT) in patients with localized soft tissue sarcoma of the extremity at high risk for local recurrence after limb-sparing surgery.
Patients and Methods: 28 patients treated between 1989 and 1999 were evaluated retrospectively. Patients presented with locally recurrent (n = 17), T2 (n = 20), high-grade (n = 26), or incompletely resected tumors (n = 11). All patients underwent limb-sparing surgery and IORT (median dose of 15 Gy) given either with high-dose-rate brachytherapy or a linear accelerator. 25 patients received additional EBRT with a mean of 50.6 Gy (range: 30.6–60 Gy). The mean follow-up time was 4.3 years (95% confidence interval [CI]: 3.0–5.6 years).
Results: The 5-year overall and distant disease-free survival rates were 66% and 54%, respectively. The overall actuarial recurrence rate after 5 years is 16% (95% CI: 1%, 31%). The crude rate after 8 years is 18%. Surgical margin status, primary versus recurrent tumor and tumor stage did not show any statistically significant influence (univariate analysis) on local recurrence rates. Patients with T1 tumors exhibited a borderline significant (p = 0.053) better distant disease-free survival (83%) compared to T2 tumors (43%). Five (24%) grade 3–4 late side effects were observed.
Conclusion: In patients with high-risk soft tissue sarcomas, IORT ± EBRT after limb-preserving surgery achieves high local control rates. The risk of normal tissue toxicities is comparable to conventional limb-sparing treatment.

Key Words: Soft tissue sarcoma · Intraoperative radiotherapy · Radiotherapy · Functional outcome · Local tumor control

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Intraoperative Strahlentherapie von Weichteilsarkomen der Extremitäten

Ziel: Beurteilung der Behandlungsergebnisse nach intraoperativer Strahlentherapie (IORT) ± perkutane Strahlentherapie (EBRT) bei Patienten mit nicht metastasierten Weichteilsarkomen der Extremitäten, die ein hohes Lokalrezidivrisiko nach extremitätenerhaltender Operation hatten.
Patienten und Methodik: Zwischen 1989 und 1999 wurden Daten von 28 Patienten retrospektiv ausgewertet. Lokalrezidive (n = 17), T2- (n = 20), „high-grade-" (n = 26) oder nicht in sano resezierte Tumoren (n = 11) wurden eingeschlossen. Alle Patienten wurden einer extremitätenerhaltenden Operation und einer IORT (mediane Dosis 15 Gy) unterzogen, die entweder als High-Dose-Rate-Brachytherapie oder mittels Linac appliziert wurde. 25 Patienten erhielten zusätzlich eine EBRT mit 50,6 Gy mittlerer Dosis (Spanne: 30,6–60 Gy). Die mittlere Nachbeobachtungszeit betrug 4,3 Jahre (95%-Konfidenzintervall [CI]: 3–5,6 Jahre).
Ergebnisse: Die 5-Jahres-Gesamtüberlebensrate und die fernmetastasenfreie Überlebensrate (DDFS) lagen bei 66% und 54%. Die aktuarische Lokalrezidivrate nach 5 Jahren beträgt 16% (95%-CI: 1%, 31%), die unkorrigierte Rate nach 8 Jahren 18%. Resektionsstatus, Primärtumor versus Rezidiv und Tumorstadium zeigten keinen signifikanten Einfluss (univariat) auf das Lokalrezidivrisiko. Patienten mit T1-Tumoren hatten ein höheres (p = 0,053) DDFS (83%) als Patienten mit T2-Tumoren (43%). Fünf (24%) Späteffekte Grad 3–4 wurden beobachtet.
Schlussfolgerung: Patienten mit Weichteilsarkomen der Extremitäten, die ein hohes Lokalrezidivrisiko haben, können durch IORT ± EBRT in hohem Prozentsatz lokal kontrolliert werden. Das Risiko von Normalgewebsschäden ist vergleichbar jenem bei konventionellen Behandlungsmethoden.

Schlüsselwörter: Weichteilsarkom · Intraoperative Strahlentherapie · Strahlentherapie · Funktionales Behandlungsergebnis · Lokale Tumorkontrolle

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Introduction

In patients with soft tissue sarcoma of the extremity at high risk for local recurrence, the current standard treatment consists of limb-sparing surgery and external-beam radiotherapy (EBRT; either pre- or postoperatively) achieving 5-year actuarial local control rates of 74–87% [8, 9, 14, 27]. Therapists are faced with the dilemma of minimizing the risk of local recurrence, which negatively affects prognosis [5, 16], and at the same time preserving maximal function of the extremity. The rationale behind intraoperative radiotherapy (IORT) is the possibility to apply a single high dose with enhanced biological effectiveness resulting in sterilization of microscopic disease of the tumor bed. In a prospective randomized trial of retroperitoneal sarcomas it has been shown that local tumor control rates could be significantly improved combining IORT with low doses of EBRT [24]. A further advantage is the possibility of direct evaluation of the extent of the tumor bed as well as organs at risk by the surgeon and the radiation oncologist. The treatment volume is limited, thus sparing surrounding healthy tissue. This should lead to less fibrosis and improved sparing of joints in tumors adjacent to joints and, finally, to a better functional outcome.

The aim of this study was to evaluate patients with soft tissue sarcoma of the extremity, combining intra- and postoperative radiotherapy, with special regard to local control, side effects, and limb function.

Patients and Methods

From June 1989 to June 1999, 28 patients with localized soft tissue sarcoma of the extremity without evidence of distant disease received IORT as part of an interdisciplinary treatment protocol of the Departments of Radiation Oncology, Orthopedic Surgery and Plastic Surgery. IORT was applied in patients in whom close or positive margins were expected, in recurrent tumors or tumors adjacent to joints with the aim of extremity-preserving treatment. Patient demographics, tumor characteristics, treatment factors, and course of disease were evaluated retrospectively by reviewing the patients' hospital files and interviewing the patients, their relatives and primary care physicians. Side effects were judged according to the LENT SOMA score [12, 13]. Extremity function was analyzed with a standard questionnaire and physical examination. The questionnaire was designed considering the functional grading system described by Kinsella et al. [10] with special regard to exercise tolerance, independence in daily life and need of medical devices.

Patient Population

Patient demographics and tumor characteristics are summarized in Table 1. There were 17 males and eleven females, with a mean age of 56 years (range: 20–84 years) at the time of definitive treatment. Of the 28 patients, 17 presented with locally recurrent, 20 with T2, ten with G2, and 16 with G3 tumors.

Table 1. Demographic data and tumor characteristics.

Tabelle 1. Demographische Daten und Tumorcharakteristika.

Characteristics		n	(%)
Age (years)			
Mean (range)	56 (20–84)		
Gender			
Male		17	61
Female		11	39
Tumor			
Primary		11	39
Locally recurrent		17	61
Histology			
Malignant fibrous histiocytoma		11	40
Liposarcoma		7	25
Schwannoma		3	10.5
Synovial sarcoma		2	7
Fibrosarcoma		2	7
Leiomyosarcoma		1	3.5
Extraosseous osteosarcoma		1	3.5
Chondrosarcoma		1	3.5
T-stage			
T1		8	29
T2		20	71
Tumor volume (ml)			
Median (range)	119 (4–2,153)		
Grade			
G1		1	3.5
G2		10	36
G3		16	57
Unknown		1	3.5
Surgical margins			
Microscopically negative		17	61
Microscopically positive (< 2 mm)		9	32
Macroscopically positive		2	7

The most common histological subtype was malignant fibrous histiocytoma (eleven patients). Tumors of eleven patients were incompletely resected with microscopically or macroscopically positive margins or with close margins. The latter was defined as tumor present within < 2 mm from the inked margin.

Treatment Factors

All patients underwent limb-sparing surgery followed by IORT. All but three patients received EBRT postoperatively. Table 2 lists surgical techniques and details of radiation treatment.

Between 1989 and 1993, 16 patients received IORT with a moulage technique ("flab method"), a high-dose-rate afterloading technique developed in our department. Irradiation was applied with a ^{192}Ir source loaded into catheters placed in flexible tissue-equivalent material as applicator [11]. For an optimal dose distribution, close contact of the flab with the tumor bed was mandatory with regard to the steep dose fall-off. This technique is different from intraoperatively placed plastic catheters which are loaded postoperatively [4].

Table 2. Treatment factors. EBRT: external-beam radiotherapy; IORT: intraoperative radiotherapy.

Tabelle 2. Behandlungsparameter. EBRT: perkutane Strahlentherapie; IORT: intraoperative Strahlentherapie.

		n	(%)
Surgical techniques			
Compartmental resection		7	25
Wide excision		15	54
Local excision		5	18
Unknown		1	3
IORT techniques			
Flab		16	57
Linear accelerator		12	43
IORT dose (Gy)			
Mean	14.5		
Range	12–15		
EBRT dose (Gy)			
Mean	50.6		
Range	30.6–60		

After 1993, IORT was applied in part with a linear accelerator (Siemens Mevatron) using 8- to 10-MeV electrons, installed in a special operating room (twelve patients).

IORT doses were 12–15 Gy with a mean of 14.5 Gy, calculated to the flab surface (15 Gy at flab surface correspond to approximately 10 Gy at 5 mm tissue depth) or the 90% isodose, respectively. 25 patients received postoperative radiotherapy with a mean of 50.6 Gy (range: 30.6–60 Gy) within a mean of 39 days (range: 21–83 days) after surgery and IORT. Three patients did not receive any EBRT. In two patients this was due to previous treatment with 60 Gy to the primary tumor site; one patient underwent compartment resection and no further treatment was considered necessary.

Follow-Up and Statistics

The time of follow-up was calculated from the end of the entire treatment, i.e., the last day of EBRT or the day of surgery and IORT. With the last evaluation performed in June 2001, the mean follow-up time was 4.3 years (95% confidence interval [CI]: 3.0–5.6 years).

5-year actuarial rates for local disease-free survival, overall survival and overall distant disease-free survival were evaluated using the Kaplan-Meier method with calculation of the 95% CI. Statistical differences in local recurrences as well as differences in survival rates were tested with the log rank. P-values were two-sided; a p-value < 0.05 was considered statistically significant.

Results

Local Control and Survival

The actuarial 5-year overall and distant disease-free survival rates are 66% (47%, 85%) and 54% (34%, 74%; Figure 1), respectively. Five local recurrences were observed, of which four occurred within 18 months and one 5.3 years after therapy. The overall actuarial recurrence rate after 5 years is 16% (1%, 31%) and after 8 years 24% (4%, 44%). The crude rate after 8 years is 18%. Surgical margin, primary versus recurrent tumor and tumor stage did not show any statistically significant influence on local recurrence rate (Table 3).

Patients with T1 tumors exhibited a borderline significant ($p = 0.053$) better distant disease-free survival (83%) compared to T2 tumors (43%) without any statistically significant difference in overall survival (Table 3). Resection margin and grading did not reveal any significant influence on disease-free or overall survival.

The time interval between surgery/IORT and EBRT had no influence on local recurrence rates or overall survival (data not shown).

Side Effects

As for acute side effects, five patients (18%) developed impaired wound healing, two requiring reoperation and one discontinuation of EBRT. In three patients impaired wound healing was managed successfully with conservative treatment. Five patients showed lymphedema and three patients grade 2–3 skin reactions (Table 4).

As for late side effects, evaluable in 21 patients, eight presented with grade 1–2 contracture, eleven with grade 1–2 pain, one with neuropathy, and two with pathologic fractures. In total, five (24%) grade 3–4 late side effects were observed in four patients.

One patient suffering a neuropathy and a pathologic fracture was an 84-year-old woman with a recurrent tumor of the distal upper extremity, who declined an amputation and in

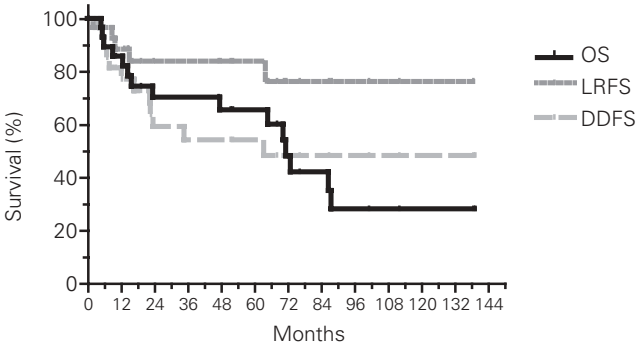

Figure 1. Overall (OS), local recurrence-free (LRFS) and distant disease-free (DDFS) survival, shown as a function of time after the end of treatment (surgery, intraoperative radiotherapy ± external-beam irradiation).

Abbildung 1. Gesamtüberleben (OS), lokalrezidivfreies Überleben (LRFS) und fernmetastasenfreies Überleben (DDFS), dargestellt als Funktion der Zeit nach Abschluss der Therapie (Operation, intraoperative Strahlentherapie ± perkutane Strahlentherapie).

Table 3. Actuarial 5-year local recurrence, overall and distant disease-free survival (DDFS) rates relating to treatment and tumor parameters. CI: confidence interval.

Tabelle 3. Aktuarische 5-Jahres-Raten von Lokalrezidiven, Gesamtüberleben und fernmetastasenfreiem Überleben (DDFS) in Abhängigkeit von Behandlungsparametern und Tumorcharakteristiken. CI: Konfidenzintervall.

Variable	Local recurrence rate		Overall survival		DDFS	
	%	(95% CI)	%	(95% CI)	%	(95% CI)
T-stage						
T1	13	(0, 36)	100		83	(53, 100)
T2	18	(0, 37)	52	(29, 75)	43	(19, 67)
Grading						
G2	0		71	(43, 99)	71	(53, 99)
G3	28	(5, 51)	45	(16, 74)	45	(16, 74)
Tumor						
Primary	9	(0, 26)	64	(38, 88)	48	(21,75)
Recurrence	26	(0, 42)	68	(42, 94)	60	(29, 91)
Resection status						
R0	17	(0, 34)	69	(46, 92)	56	(33, 79)
R1[a]	13	(0, 36)	57	(20, 94)	53	(13, 93)
IORT technique						
Flab	7	(0, 21)				
Electrons	29	(0, 58)				

[a] including R1 *and* R0 with narrow margins (1–2 mm)

whom an epineurectomy and a periostectomy with partial bone resection were performed. She received 15 Gy intraoperatively and 46 Gy EBRT. The fracture was successfully treated conservatively and she remained recurrence-free for 5.9 years, when she died of a non-tumor-related condition. The second patient with a pathologic fracture was a 60-year-old man, also with a recurrent distal upper extremity tumor, who underwent a compartment resection and received 15 Gy intraoperatively and 60 Gy EBRT. The fracture healed after conservative treatment and he remains disease-free after almost 8 years.

Table 4. Acute and long-term side effects (grading according to LENT/SOMA criteria).

Tabelle 4. Akute und späte Nebenwirkungen (nach LENT/SOMA-Kriterien).

Side effect	Grade	n	(%)
Impaired wound healing		5	18
Acute lymphedema		5	18
Skin reactions		3	12
Chronic lymphedema	1–2	11	52
Fibrosis	1–2	15	71
Contracture	1–2	8	38
Contracture	3	2	10
Pain	1–2	11	52
Neuropathy	3	1	5
Pathologic fractures	4	2	10

Functional Outcome

The function of the treated extremity could be judged in 22 patients. Eight patients (36%) had no functional limitations, neither recreational nor occupational, and were able to participate in prolonged activities, i.e., going on longer hiking tours, skiing, swimming, etc. Five patients (23%) with minor restrictions required infrequent support in daily life. Nine patients (41%) showed limitations necessitating regular help in daily life, i.e., orthotic devices (walking canes or braces) or assistance for tasks like buttoning, writing, or lifting.

Discussion

Local Control

Actuarial 5-year local recurrence-free survival was 84% in our cohort of patients who received IORT and postoperative EBRT. Rachbauer et al. [19] recently published results of a prospective study of 39 patients with soft tissue sarcoma treated with the same flab technique intraoperatively, combined with pre- or postoperative EBRT. Their actuarial 2-year local control rate was 100% and the disease-free survival 84%. Pisters et al. [18] described an 82% actuarial local control rate after 5 years for patients who received limb-sparing surgery and 42–45 Gy brachytherapy alone. It should be made clear that Pisters et al. used low-dose-rate brachytherapy alone after complete (R0) resection as an adjuvant treatment which is not the same as IORT.

After limb-sparing surgery with *intraoperative brachytherapy* or *intraoperative electron-beam radiotherapy* and EBRT, local control rates of 90–100% have been reported [1, 6, 7].

In our small number of patients, the time interval between surgery/IORT and start of EBRT had no influence on treatment outcome. Patients with Ewing's sarcoma (n = 156) treated in the CESS 86 and EICESS 92 trials were evaluated in a retrospective analysis [22]. No influence of the postoperative time interval before start of EBRT was found on local control rates or event-free survival.

Side Effects

In this study, five patients (18%) presented with impaired wound healing, of whom two (7%) required reoperation. Saddegh & Bauer [21] and Skibber et al. [25] described 34–40% impaired wound healing after surgery alone with 8–16% reoperations. O'Sullivan et al. [17] reported 35% of impaired wound healing after preoperative radiotherapy and surgery versus 17% after surgery and postoperative radiotherapy. Alektiar et al. [2] observed a complication rate of 17% after surgery and brachytherapy alone versus 15% without brachy-

therapy, if at least 5 days were allowed for loading the catheters postoperatively. Their reoperation rate was 10% versus 0% (surgery alone). Delannes et al. [6] found 34% wound-healing impairment after surgery with IORT and EBRT. Eble et al. [7] reported on a 12% complication rate with 4% reoperations.

A 24% incidence of late grade 3–4 side effects was observed in this report as compared to a 6–36% incidence in published studies. Stinson et al. [26] found 36% skin reactions, especially associated with application of chemotherapy, 6% bone fractures, 20% contractures associated with joint irradiation, 7% pain requiring narcotics, 19% edema (grade 2+), and 57% tissue indurations. Complication rates were mainly dependent on the total dose and treatment volume. Robinson et al. [20] found 72% of patients with significant limitations in joint movement, 65% suffering from moderate pain requiring no or low-dose analgetic treatment, 39% swelling of the leg, and 69% fibrosis depending on radiotherapy dose and treatment volume.

In two older patients, a pathologic fracture developed after periosteal excision with or without partial bone resection. This phenomenon is attributed to both periosteal excision and radiation compromising vascularity and removing osteoprogenitor cells. Lin et al. [15] described a 9% overall risk of pathologic fracture at 5 years after EBRT and/or brachytherapy. On multivariate analysis, an increased risk of pathologic fractures in patients undergoing periosteal stripping and radiotherapy was found. Female gender and prior chemotherapy were, in contrast to radiotherapy alone, additional risk factors. The pathologic fracture rate of this study is in accordance with data from the literature (0–8%) [2, 3, 6, 7, 14, 26].

Only one neuropathy was observed in this study. It could not be distinguished whether this could be attributed to the surgical procedure with epineurectomy or radiotherapy or both. The incidence of neuropathy described in the literature is 2–12% with 7% after surgery alone [2], 2–3% after surgery and EBRT [3, 14], 7% after surgery and adjuvant brachytherapy [2], and 4–12% after surgery, IORT and EBRT [6, 7].

Overall, the risk of normal tissue toxicities is comparable to conventional limb-sparing treatment. Due to the small number of patients and the insufficient or nonuniform description of side effects in other studies, however, the comparison with published data of the incidence of late side effects is difficult.

Function of the Extremity

59% of patients had no or minor impairment in limb function without needing any regular help or aid in everyday life. 41% had major deficits in limb function needing, e.g., walking aids or splints regularly. No direct comparison to historical data is possible as far as function of the limb is concerned. Stinson et al. [26] report that after surgery and EBRT 84% of patients are ambulating without assistive devices and with mild or no pain. Robinson et al. [20] saw a normal function in 50% of patients; 15% needed a walking aid. Worse function was associated with higher radiotherapy doses > 60 Gy, unconventional fractionation, female gender, and age. Schupak et al. [23] found a similar functional outcome in patients undergoing surgery ± adjuvant brachytherapy. Delannes et al. [6] detected functional impairment in 19% of patients after surgery with IORT and EBRT.

Conclusion

High local control rates can be achieved with IORT and EBRT in soft tissue sarcomas of the extremity at increased risk of local recurrence. Functional outcome was good in the majority of patients. The risk of normal tissue toxicities is comparable to conventional limb-sparing treatment.

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