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CLINICAL INVESTIGATION **Sarcoma**

INTRAOPERATIVE ELECTRON-BEAM THERAPY FOR PRIMARY AND RECURRENT RETROPERITONEAL SOFT-TISSUE SARCOMA

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Purpose: This study assesses the long-term outcome of patients with retroperitoneal soft-tissue sarcomas treated by maximal resection in combination with intraoperative electron-beam therapy (IOERT) and postoperative external-beam radiotherapy.

Methods and Materials: From 1991 to 2004, 67 patients were treated with curative intent for primary ($n = 26$) or recurrent ($n = 41$) retroperitoneal soft-tissue sarcoma. All patients underwent maximal resection in combination with IOERT (mean dose, 15 Gy), 45 patients underwent additional postoperative EBRT, and 20 patients were previously irradiated.

Results: The 5-year actuarial overall survival (OS), disease-free survival, local control (LC), and freedom from metastatic disease of all patients was 64%, 28%, 40%, and 50%, respectively. The 5-year LC inside the IOERT field was 72%. For patients who completed IOERT and EBRT after R0-resection 5-year and 10-year OS was 80%, and 5-year and 10-year LC was 100%. Only 1 of the 21 patients after R0-resection and only 8 of 34 patients after R1-resection compared with 9 of 12 patients after R2-resection experienced inside IOERT–field relapse. Grade II or higher late complications were seen in 21% of the patients, but only 2 patients required surgical intervention because of late complications.

Conclusion: In selected patients, IOERT results in excellent local control and survival, with acceptable morbidity.

Retroperitoneal sarcoma, Soft-tissue sarcoma, Intraoperative radiotherapy, Radiotherapy, Local control.

INTRODUCTION

The retroperitoneal space is the site of origin for 15% to 20% of soft-tissue sarcomas (STSs) (1, 2). Patients affected often present with large, locally advanced tumors, as symptoms occur late because of the general mobility of the retroperitoneal viscera and the large volume of space available for organ displacement. Complete surgical resection remains the mainstay of treatment but is possible in less than 70% of patients who present with primary disease (2, 3). Moreover, as a consequence of the aforementioned late tumor presentation, wide surgical resection with microscopically negative margins is usually not possible (4). Consequently, local recurrence rates are high (5–8).

Randomized trials have demonstrated that the addition of radiation to surgery unequivocally improves local tumor control for patients with extremity and superficial trunk STSs (3, 9, 10). This finding has led to considerable interest in the use of surgery plus radiation for patients with retroperitoneal STSs (2). The efficacy of postoperative external-beam irradiation (EBRT) is limited by the inability to deliver adequate doses of irradiation on account of the dose tolerance limits of small bowel, spinal cord, stomach, kidney, and liver (11). The experience with extremity STSs shows that a high probability of local control can be achieved with doses of 60 to 70 Gy (12, 13). Intraoperative electron-beam radiotherapy (IOERT) in combination with EBRT and surgery has been used in the management of these tumors to overcome these dose limitations (14–19). This report reviews the results of the combination of maximal resection with IOERT and postoperative EBRT in 67 consecutive patients treated with curative intent for primary and recurrent retroperitoneal STS.

PATIENTS AND METHODS

Between 1991 and 2004, more than 1,300 patients were treated with an intraoperative electron boost (IOERT) in Heidelberg, 320 of which suffered from STSs. These tumors were located in the

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retroperitoneal space in 67 cases of traceable adult patients. Preoperative investigation included physical examination and computerized tomography (CT) or magnetic resonance imaging (MRI) of the tumor site, the chest, and the abdomen. Indication for IOERT plus EBRT in patients with retroperitoneal STS is seen, when in tumors larger than 5 cm, grade higher than 2, or recurrent tumors, maximal resection with microscopically clear margins of at least 1 cm is not likely to be achieved, and systemic spread is either excluded or does not prevent an overall curative intent. Forty-five patients underwent maximal resection and IOERT plus additional EBRT. Twenty-two patients underwent maximal resection and IOERT only. Of these patients, 20 patients with recurrent tumors were previously irradiated (mean dose, 45 Gy; range, 39.6–59.4 Gy) and 2 patients declined postoperative EBRT.

Mean age of the patients (male:female = 35:32) included in this analysis was 54 years (range, 17–74 years); 39% of patients experienced primary STS and 61% experienced recurrent STS. In 13% of patients distant spread (1 to 3 lesions) was known at the time of surgery. Complete tumor resection with microscopically clear margins was possible in only 31% of the treated patients. Multivisceral resection of contiguous organs was performed on 31 patients (46%). Surgical clips were used to clearly demarcate the boundaries of the IOERT field. For further patient characteristics, see Tables 1 and 2.

Table 1. Patient characteristics

Characteristic	*n*	%
Tumor		
Primary	26	39
Recurrent	41	61
Radiotherapy		
IOERT only	22	33
IOERT + EBRT	45	67
R-status		
R0	21	31
R1	34	51
R2	12	18
Grading		
G1	4	6
G2	18	27
G3	45	67
Size		
<5cm	15	22
5–10 cm	23	34
10–20 cm	19	29
>20 cm	10	15
Histology		
Liposarcoma	34	51
Leiomyosarcoma	10	15
Malignant fibrous histiocytoma	7	10
Other	16	24
Staging*		
Stage IB	4	6
Stage IIA	15	22
Stage IIB	0	0
Stage III	39	58
Stage IV	9	13

Abbreviations: EBRT = external-beam radiotherapy; IOERT = intraoperative electron-beam radiotherapy.

* Data are from American Joint Commitee on Cancer. Soft tissue sarcoma. In: Green FL, Page DL, Fleming ID, editors. AJCC cancer staging manual, 6th ed. New York:Springer-Verlag: 2002. p. 193–200.

Median follow-up was 30 months (range, 6 to 170 months), and median follow-up for surviving patients was 41 months. Follow-up examinations were routinely performed in our institution, either in the surgery department or in the radiation oncology department, and included clinical examination, chest X-ray, and CT or MRI of the initial tumor site. Nineteen patients who were lost to routine follow-up in our institution were contacted via mail and asked to fill in a questionnaire, which was returned by 16 patients.

The location of recurrence was classified as IOERT-in-field, marginal, or out-of-field failure after review of the diagnostic workup and radiation reports.

Acute toxicity was assessed by application of CTC, and late toxic effects were scored via EORTC/RTOG criteria. Toxicities from surgery, IOERT, and EBRT were pooled together because of the difficulty of precisely determining the contributing factors for each separate treatment.

Median IOERT dose was 15 Gy (range, 12–20 Gy), and median EBRT dose was 45 Gy (range, 20–59.4 Gy). The median interval between IOERT and EBRT was 35 days (range, 14–45 days).

Intraoperative electron-beam radiotherapy was performed in a dedicated operation theater with an integrated Siemens Mevatron linear accelerator (Siemens, Concorde, CA), which provides fast electrons between 6 and 18 MeV, and thus covers a depth of up to 6 cm, if necessary. IOERT dose is prescribed to the 90% isodose. The IOERT volume covered the tumor bed with a safety margin of 1 to 2 cm and is marked by surgical titanium clips to make further external-beam treatment planning easier. Median field size of IOERT was 13 cm (range, 7 × 7 cm to 28 × 11 cm). Median electron energy was 9 MeV (range, 6–15 MeV). Further details on our IOERT technique have been published elsewhere (20–22).

Electron-beam radiotherapy was applied postoperatively via linear accelerator (Siemens) (18-MV and 23-MV Photons), by use of 3D-conformal treatment planning routinely since 1998. Dose prescription followed the International Commission on Radiation Units and Measurements, Report No. 50 (ICRU Report 50, 1993).

Descriptive statistics, two-by-two tests, and Kaplan-Meyer estimation analysis were applied for statistical workup. Five-year actuarial rates for overall survival, local disease-free survival, distant relapse-free survival, and distant relapse-free survival were evaluated using the Kaplan-Meier method, with calculation of the 95% CI by application of Statistica version 5.5 (StatSoft, Inc., Tulsa, OK). Statistical differences in local recurrences as well as survival rates were tested by the log-rank test with patient's age, tumor size, resection margin, tumor grading, histologic subgroups, IORT dose of 15 Gy or higher, EBRT dose of of 45 Gy or higher, and primary vs. recurrent situation as variables. p Values were two-sided, and a p value of less than 0.05 was considered statistically significant.

RESULTS

All patients underwent maximal tumor resection and IOERT; 31% had a complete resection (R0), 51% had microscopically residual disease (R1), and 18% had macroscopically residual tumor (R2). For the entire group of patients, the 1-year, 2-year, 5-year, and 10-year actuarial overall survival rates were 91%, 83%, 64%, and 58%, respectively (Fig. 1). The only factor with significant impact on survival was resection status, with a 5-year overall sur-

Table 2. Patient demographics

Parameter	Studies				
	Stoeckle *et al.* (8)	van Dalen *et al.* (7)	Lewis *et al.* (6)	Gronchi *et al.* (5)	Our data
No. of patients	165	142	500	167	67
Male:female ratio	1.0:1.2	1.0:1.22	1.34:1.0	1.2:1.0	1.1:1.0
Age (years)					
Median	54	60	58	53	54
Range	16–82	18–88	16–88	15–82	17–74
Location					
Abdomen	70	–	–	–	–
Pelvis	30	–	–	–	–
Tumor size (cm)					
Median	15	–	–	–	14.7
Range	2–70	–	–	–	3–51
AJCC stage (%)					
T1	6	–	6	–	22
T2	94	–	85	–	78
NS		–	9		
N0	95	–	–	–	–
N1	5	–	–	–	–
Grade (%)					
Low	16	45	36	35	6
Intermediate	41	36			27
High	43	16	64*	65*	67
NS		3			
Histology (%)					
Liposarcoma	26	38	41	57	51
Leiomyosarcoma	23	29	27	17	15
MFH	17	–	7	8	10
Other	34	33	22	10	24

Abbreviations: AJCC = American Joint Committee on Cancer; MFH = malignant fibrous histiocytoma; NS = not stated.
* Grade 2–3.

vival of 87% for R0-resected patients and 50% for R1/R2-resected patients ($p < 0.01$). The 1-year, 2-year, 5-year, and 10-year actuarial locoregional (abdominal) control rates were 78%, 62%, 40%, and 33%, respectively (Fig. 2). The 5-year local-control rate inside the IOERT field was 72%. Of the 40 patients with abdominal recurrence, 34 underwent relaparotomy, 19 of which were treated with a second IOERT session (mean dose, 15 Gy). In 24 patients, a macroscopic complete resection was performed. Five-year disease-free survival and freedom from metastatic disease were 28% and 50%, respectively.

Abdominal control was significantly affected by resection status (R0 vs. R1/2, $p < 0.001$), grading (Grade 1/2 vs. Grade 3, $p < 0.008$), and primary vs. recurrent disease ($p < 0.001$). In patients with primary disease, 5-year locoregional control was 64% compared with 15% in patients with recurrent disease ($p < 0.015$). For the 12 patients who completed IOERT and EBRT after R0-resection, 5-year and 10-year actuarial survival was 80%, and 5-year and 10-year locoregional control was 100%. For the 12 patients with R2-resection, 5-year locoregional control was 0%. One of the 21 patients after R0-resection and only 8 of 34 patients after R1-resection compared with 9 of 12 patients after R2-resection experienced inside IOERT–field relapse.

Postoperative wound-healing disturbances were seen in 5 patients. In none of these cases could wound-healing disturbances be attributed to the IOERT-field. Grade 2 or higher late complications were seen in 21% of the patients, but only 2 patients required surgical intervention because of late complications. Three patients experienced GI fistulas, 4 experienced small-bowel stenosis, 5 experienced neuropathy, and 2 experienced urethral stenosis (Table 3).

DISCUSSION

The present retrospective analysis was performed from a compiled database of 67 consecutive patients with primary or recurrent retroperitoneal sarcomas, seen in a single institution between 1991 and 2003, with the same and predefined treatment policy. The overall survival rate at 10 years after combined definitive surgery, IOERT, and EBRT was 58%, and the 5-year disease-free survival and local recurrence–free survival was 28% and 40%, respectively. The results, considering the patients characteristics (Table 2), compare favorably or equally with the main published experiences (Tables 4 and 5), even though, as in other series, the relatively poor prognosis for patients with retroperitoneal sarcoma depends largely on the failure of locoregional control.

Surgery remains the only curative treatment modality in patients with retroperitoneal sarcoma. Although complete resection affords the best opportunity for survival, this treat-

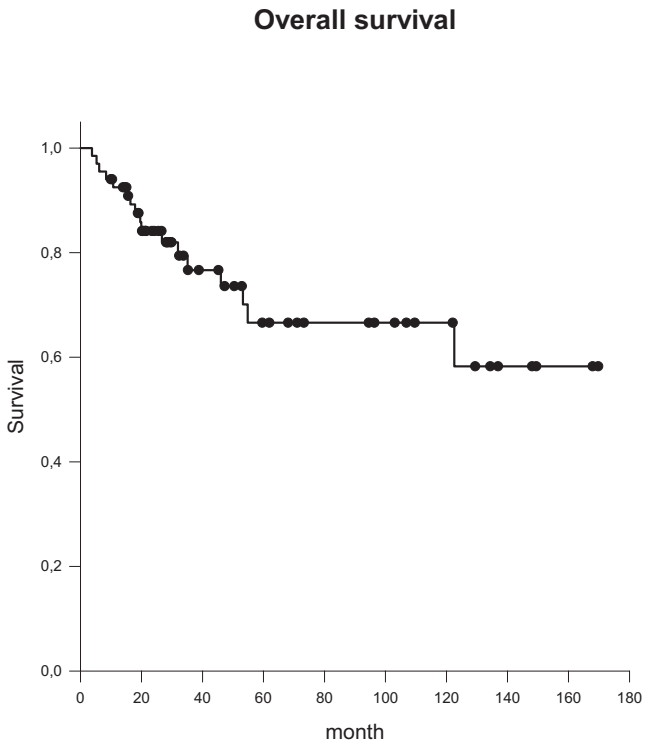

Fig. 1. Actuarial overall survival of all patients.

ment can be accomplished in only approximately 50% of all patients. Storm *et al*. (23) found a compete resection rate of only 53% in a review of cumulative series of 560 patients undergoing explorative laparotomy. A low rate of initially

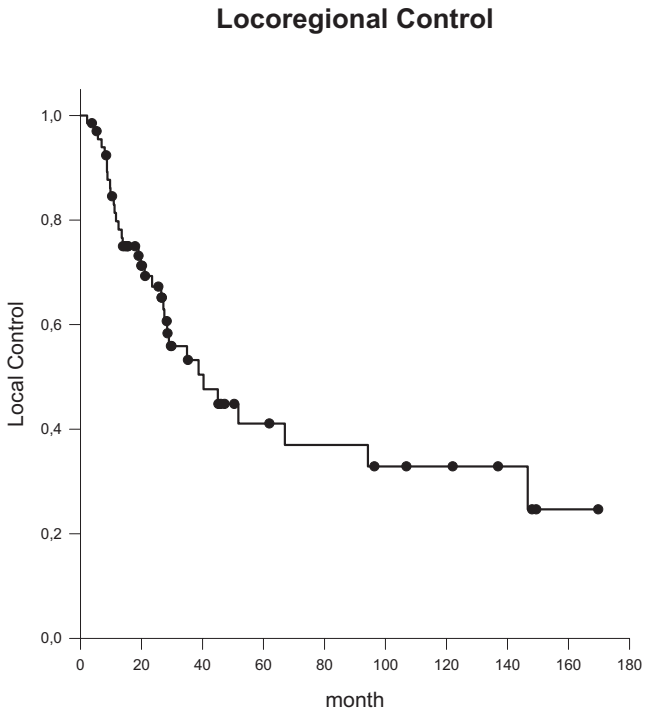

Fig. 2. Intra-abdominal/retroperitoneal actuarial local control of all patients.

Table 3. Incidence of acute and late toxicity

Acute toxicity	Wound healing disturbances	7%
	GI (CTC >2)	13%
Late toxicity	Gl fistulae	4.5%
(≥ Grade 2)	Small-bowel stenosis	6%
	Neuropathy	7.5%
	Ureteral stenosis	3%

Two patients required surgical intervention because of late complication.

complete resection is also found in our series. Of the patients referred to the University of Heidelberg for evaluation, only 31% had a complete resection of their tumors in the initial surgery. Even after complete resection, most authors report mean locoregional recurrence rates for retroperitoneal STS of approximately 50% (5–8). Randomized trials have demonstrated that the addition of radiation to surgery unequivocally improves local tumor control for patients with extremity and superficial trunk STS (3, 9, 10). Stoeckle *et al*. (8) found a significant reduction of local recurrence from the patients with retroperitoneal STS who received an adjuvant radiotherapy. Dose escalation seems to improve local control in STS. Tepper *et al*. (24) demonstrated that only 18% of patients who received less than 50 Gy achieved local control compared with 83% of those who received a dose greater than 60 Gy. Fein at al (12) reported similar findings, with improvement of local control with dosages greater than 55 Gy. However, postoperative radiotherapy is limited by the tolerance of the surrounding healthy tissues, and EBRT doses that exceed 45 to 50 Gy are rarely administered. The experience with extremity STSs shows that doses above 60 Gy are necessary to achieve a high probability of local control (12, 13). This dose far exceeds the tolerance of the surrounding normal structures such as small intestine, spinal cord, stomach, kidneys, and liver (11).

Even with the most sophisticated treatment planning, the dose that can be safely delivered by EBRT remains limited. Intraoperative irradiation is a possibility to overcome these limitations and to escalate the dose in retroperitoneal regions most likely to harbor residual disease (14). The impact of the high single dose applied by an intraoperative electron boost (as well as HDR-brachytherapy) is not fully understood. Taking the linear-quadratic equation as a basis, with different α/β values for tumor cells and early and late risk-organ reactions, the biologic effectivity of the high single intraoperative dose varies between 2 and 3.5 times the IOERT dose in conventional fractionation. However, the clinical application of this calculation is limited because of a lack of precise values of α/β and can only provide an estimation (25, 26). However, in combination with EBRT, equivalent doses of 70 Gy or more can be achieved, with the potential of sterilizing potential residual tumor cells and, thus, improve local control in retroperitoneal STS (11).

The current approach at the University of Heidelberg is maximal resection, and, if technically feasible, IOERT is

Table 4. Treatment outcomes

Parameters	Stoeckle *et al.* (8)	Van Dalen *et al.* (7)	Lewis *et al.* (6)	Gronchi *et al.* (5)	Our data
No. of patients	165	142	278	167	67
Dates	1980–1994	1989–1994	1982–1997	1982–2001	1991–2003
Median follow-up (months)	ND	86	22*	65	30[†]
Prior treatment (%)					
Untreated	100	ND	100	49	39
Recurrent	0	ND	0	51	61
Distant metastases (%)					
M0	88	100	100	100	87
M1	12	0	0	0	13
Macroscopic total resection (%)	65	54	67	ND	
R0					31
R1					51
R2					18
Five-year local control (%)	42[‡§]	32[§]	59[‖]	48	40[¶]
Five-year DMFS (%)	67[#]	ND	79[‖]	48	50
Five-year survival (%)	46	ND	54[‖]	54	62
Five-year DFS (%)	ND	ND	ND	28	28

Abbreviations: DFS = disease-free survival; DMFS = distant metastasis–free survival; ND = no data available.
* The median follow-up was 40 months for survivors.
† The median follow-up was 41 months for survivors.
‡ Crude percentage.
§ Outcome for 114 complete resected patients.
‖ Outcome for 231 patients who underwent resection; the survival is cause specific.
¶ Abdominal/retroperitoneal control.
# Outcome for 94 complete resected initial M0 patients.

employed in patients who meet the above mentioned criteria. Only 1 randomized study of IOERT for retroperitoneal sarcoma has been conducted by the NCI (27), which included 35 patients. Fifteen patients received 20-Gy IOERT followed by postoperative EBRT to 35 to 40 Gy. Twenty patients received standard postoperative EBRT in the range of 50 to 55 Gy. The follow-up report, with a median follow-up of 8 years, showed significant improvement in local control, with a failure rate of 40% in the IOERT group and 90% in the control group (11). The 5-year local control and survival of 40% and 64%, respectively, in our series compares favorably with or equals other series without IORT (5–8) (Table 4) and with IORT (15–19, 28) (Table 5). The dose escalation by IOERT in the regions of residual or potentially residual disease in combination with EBRT led to an improved IOERT-in-field local-control rate of 72% for all patients and 84% after gross tumor resection, compared with 40% adominal/retroperitoneal control, similar to rates in other collectives treated with IORT. Petersen *et al.* (16) reported a 5-year IOERT-in-field local-control rate of 90%, and Gieschen *et al.* (15) reported 83% after gross tumor resection (Table 5).

On the basis of animal studies (26) and the randomized National Cancer Trial (NCI) (11), peripheral neuropathy represents the main toxicity associated with IORT. In the NCI trial, the rate of peripheral neuropathy was as high as 60%, and it was attributed to the high dose of IORT (20 Gy) and the use of abutting electron fields with potential areas of overlap. In the Mayo Clinic study, the rate of severe peripheral neuropathy was 10% (16). Alektiar *et al.* (28) reported 6% peripheral neuropathy by use of HDR-brachytherapy for intraoperative radiation therapy. In our present study, the rate of peripheral neuropathy was 7.5% (5 of 67), similar to that observed in the Mayo Clinic study (16). The lower rates in the brachytherapy IORT may be the result of a difference in dose prescription. Whereas Alektiar *et al.* (28) prescribed his dose in all cases to a 1-cm depth from the source, dose prescription in our study was meant to cover a mean depth of 3 cm (range, 1.9–5 cm) by the 90% isodose.

In an animal study, noteworthy rates of ureteral stenosis caused by the IOERT volume (29) were observed. In our series with relatively large irradiated IOERT volumes, the rate of ureteral stenosis was as low as 3% (2 of 63). Only in patients with residual disease at the ureter was this area included in the IOERT field; otherwise, it was mechanically retracted out of the treatment field or was covered by lead shields. Gieschen *et al.* (15) reported on hydronephrosis caused by ureter stenosis in 4 of 20 patients (20%). Other types of complications also compare favorable with those reported in the literature (11, 15, 16). The rate of gastrointestinal complications in our series was 10% (7 of 67) compared with 13% in the NCI trial (11), 18% in the Mayo Clinic study (16), and 19% in the MSKCC study (28). The fistula rate was 4% (2 of 67) in our study compared with 8% in the Mayo Clinic study and 9% in the MSKCC study. The question of whether an increased number of side effects of EBRT after IOERT occurred is difficult to answer in a retrospective analysis. In a comparison side effects by use of IOERT in combination with moderate-dose EBRT with side effects reported in other studies that used dose-equivalent EBRT alone, side effects seemed to be reduced. For example, Sindelar *et al.* (11) reported a 50% rate of disabling

Table 5. Treatment outcomes of IORT-treated patients with retroperitoneal STS

Parameters	Alektiar *et al.* (28)	Petersen *et al.* (16)	Gieschen *et al.* (15)	Sindelar *et al.* (11)	Our data
Treatment	Surgery/HDR-IORT 15 Gy/EBRT 45–50.4 Gy	Surgery/IOERT 15 Gy/EBRT 45 Gy	EBRT 45 Gy, Surgery, IOERT 15 Gy	Surgery; IOERT 20 Gy + EBRT 40 Gy or EBRT 50–55 Gy	Surgery/IOERT 15 Gy/EBRT 45 Gy
No. of patients	32	87	37 (20 with IOERT)	35 (15 with IOERT)	67
Dates	1992–1996	1981–1995	1980–1996		1991–2003
Median follow-up (months)	33	42*	38	96	30[†]
Prior treatment (%)					
Untreated	12	43	29		39
Recurrent	20	44	8		61
Distant metastases (%)					
M0	100	100	95		87
M1	0	0	5		13
Macroscopic total resection (%)	94	88			
R0		17	20		31
R1		64	9		51
R2		19	8		18
Five-year local control (%)	62	59[‡]	59[§]	37[‖]	40[¶]
Five-year DMFS (%)	82	57	54	NR	50
Five-year survival (%)	45	47	50	42	62
Five-year DFS (%)	55	31	38	36	28

Abbreviations: DFS = disease-free survival; DMFS = distant metastasis–free survival; NR = not reported.
* Surviving patients.
[†] The median follow-up for surviving patients was 41 months.
[‡] Five-year local control (%) inside IOERT field is 90%.
[§] Five-year local control (%) for patients (n = 16) after EBRT, gross surgical resection, and IOERT is 83%.
[‖] Five-year local control (%) for IOERT-treated patients was 60 vs. 11 in only EBRT-treated patients.
[¶] Abdominal/retroperitoneal control, 5-year local control (%) inside IOERT field is 72% for all patients, 95% for patients (n = 21) after complete resection and IOERT, and 84% for patients after gross tumor resection.

radiation-related enteritis in patients with completely resected retroperitoneal STS who were treated with postoperative radiation from 50 to 55 Gy.

As shown by our data and that of other groups, resection state has the most significant impact on local control and survival. Protocols are ongoing at several centers to determine whether preoperative chemotherapy and radiotherapy are more effective in the multimodal treatment of retroperitoneal sarcomas (30, 31). This strategy has several advantages: (1) the gross tumor volume can be defined, allowing accurate treatment planning; (2) tumors often displace radiosensitive viscera outside of the radiation field; (3) lower radiation doses may be biologically effective preoperatively; and (4) tumor shrinkage that results from preoperative treatment may lead to higher rates of complete resections. Pisters *et al.* (30) reported of a Phase I trial with preoperative chemoradiation, surgical resection, and IOERT. Macroscopic complete resection was achieved in 26 (90%) of 29 patients.

Despite the lack of clear impact of adjuvant radiation on survival in retroperitoneal sarcoma, efforts to improve local control are still warranted, given that patients with retroperitoneal STS can and do die of local recurrence. IOERT to the area of highest risk for local recurrence can improve the local-control rate. Inside IOERT–field 5-year local tumors control was significantly higher with 72% compared with only 40% abdominal/retroperitoneal control. Especially after complete macroscopic resection, IOERT in combination with EBRT seems to be able to compensate for minimal residual disease, whereas after macroscopic incomplete resection, IOERT does not improve long-term locoregional control.

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