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Prognostic Factors for Retroperitoneal Soft-Tissue Sarcoma

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ABSTRACT

Purpose: To evaluate treatment results of retroperitoneal soft-tissue sarcoma using surgery with/without postoperative radiotherapy (RT) and to identify the prognostic factors for overall and disease-free survivals.

Patients and methods: During the period 1998-2000, sixty patients with retroperitoneal sarcoma, presented to the surgical department, National Cancer Institute, Cairo University, were available for analysis. They were divided into adult and pediatric groups. Different patient's, tumor and treatment-related factors were analyzed for their influence on both overall and disease free survival. Patients had been observed for a mean period of 21±8 months (ranged from 10 to 38 months).

Results: There were 41 adults (27 male and 14 female with mean age 52±16 years) and 19 patients in the pediatric group (8 male and 11 female with mean age 5±4 years). Presentation was primary 71% and 84% of the 2 groups, respectively. In the whole group, 27 patients (45%) had tumors < 20 cm in its maximum dimension. Sixty percent (36 patients) had low-grade lesions. Complete gross resection was achieved in 40 patients (67%), while the other 20 (33%) patients couldn't be completely resected. Visceral resection was performed in 28 patients, 50% of them (14 patients) had gross residual left at the tumor bed. Forty-three patients (72%) experienced local relapse, 17 of them had distant metastases as well. The 18-month overall survival was 67% and the 18-month disease-free survival (DFS) was 38%. Female gender, age < 50 years, primary tumor, size < 20 cm, low-grade lesions, gross resection and adjuvant postoperative radiotherapy, all affected both DFS and overall survival significantly. Pathological subtypes and adjuvant chemotherapy did not show similar effects.

Conclusion: Complete surgical resection, with adjuvant radiotherapy are essential for local control which is the main objective in the management of retroperitoneal soft-tissue sarcoma.

Key Words: *Retroperitoneal sarcoma - Prognostic factors - Postoperative radiotherapy.*

INTRODUCTION

Retroperitoneal sarcomas are rare tumors. Their incidence is about 10% of all soft tissue sarcomas, constituting less than 1% of all malignant neoplasm [1]. However, they represent a formidable challenge to the treating oncologist due to their proximity to vital structures and their propensity for local relapse [2]. The prognosis for patients with these tumors is poor with reported overall 5-year survival of 15%-50%.

Surgery is the principal mode of therapy and offers the most favorable prognosis after complete resection [3]. Patients with retroperitoneal sarcomas generally had a worse prognosis than those with extremity sarcomas. Retroperitoneal soft tissue sarcomas grew to larger sizes before they become clinically apparent and they involved important vital structures that precluded surgical resection. Furthermore, the surgical margins that can be obtained around these sarcoma are often inadequate because of anatomic constraints [4]. Indeed, complete resection, defined as removal of all gross disease, can be obtained only in half of the patients [5] and in order to obtain such a resection, inclusion of adjacent organs en bloc resection is required in more than 80% of cases [6]. Furthermore, even in patients who have had complete gross resection, the rate of local relapse is quite high, with a 5-year local recurrence rate ranging from 39% [7] to as high as 72% [5]. Furthermore, these patients surviving more than 5 years had a significant local failure rate of 58% [8]. Moreover, adjuvant treatment in the form of radiotherapy was frequently limited by the tolerance

of the surrounding dose-limiting normal tissues, such as the bowel, kidneys, liver and spinal cord. Similarly, the role of adjuvant chemotherapy in retroperitoneal soft tissue sarcomas remained controversial.

In this study, we presented NCI, Cairo experience for the treatment of retroperitoneal soft tissue sarcomas and addressed the prognostic effect of patient, tumor and therapeutic factors on the overall and disease-free survival (DFS).

PATIENTS AND METHODS

Between January 1998 and December 2000, 107 patients with retroperitoneal sarcomas presented to the surgical department, National Cancer Institute, Cairo University. Out of these 107 files, 47 files lacked radiological or pathological data. Therefore, only 60 were the subject for this analysis. A retroperitoneal tumor was defined as being located posterior to the posterior peritoneum from the diaphragm to the pelvic floor. The diagnostic evaluation included history and physical examination, X-ray or CT scan of the chest and CT scan of the abdomen and pelvis. Bone scans were obtained only if any clinical suspicion of bone metastases was present. Routine preoperative laboratory tests, included complete blood count as well as liver and kidney function tests were performed in all patients.

All the 60 patients had histopathologic confirmation in the department of pathology, National Cancer Institute. Tumor was graded as either high or low according to the differentiation, cellularity and amount of stromal necrosis, pleomorphism and frequency of mitotic figures. The pathologic microscopic margins were not characterized in this study because of the nature and location of these tumors.

The study population was divided into pediatric and adult groups. For each group, factors suggested to influence the prognosis of this type of tumor were classified into three categories.

Patients' factors included:

a- Age.

b- Gender.

Tumor factors included:

a- Presentation (primary versus recurrent).

b- Size of the tumor (based on the greatest pathological dimension).

c- Tumor grade (low versus high).

Treatment-related factors included:

a- The extent of resection as judged by the operating surgeon at the end of the operation (complete versus partial). A partial resection is defined as gross residual disease left at the tumor bed. A visceral resection was defined as any organ resection including but not limited to kidney, pancreas, spleen, colon, small intestine, adrenal and stomach.

b- The use of adjuvant therapy in the form of radiotherapy and/or chemotherapy.

Radiotherapy was delivered as postoperative (PORT) adjuvant treatment. Megavoltage external photon beam, with or without electron, was used. The total dose of irradiation ranged from 40 to 66 Gy (median 50 Gy), 2 Gy/fraction, 5 fractions/week. Field arrangement was tailored according to size, extend and location of the tumor. Direct, two parallel opposing fields, or wedged filed with 2D/3D planning system were used.

Thirty-nine patients (65%) received adjuvant chemotherapy. However, it was used on a non-uniform basis as regard, indication, regimen, or number of courses.

Patients have been observed for follow up for a period ranged from 10-38 months, with a median follow-up of 19±8 months. The overall survival was calculated from the date of surgery to the date of death from disease or last follow-up. Disease-free survival (DFS) was calculated from the date of surgery to the date of progression (whether local, distant, or both). Relapse was confirmed clinically and/or radiologically using CT/MRI of the abdomen and pelvis).

Statistical analysis:

We used Stat View version 4.5 package (Abacus Concepts. Inc. Berkeley, CA). Numerical data were described in terms of means and medians for central tendency and standard deviation and range for dispersion. Chi-square test was used to compare qualitative variables. Overall survival and relapse-free survival were determined using the Kaplan-Meier product

limit method [9]. Comparison between survival rates of different groups was determined using the log-rank test [10]. Probability (p-value) of less than 0.05 was considered to be significant and less than 0.001 to be highly significant. A multivariate analysis was done using Cox-regression test. Output is represented in the form of significance, Odds ratio and its 95% confidence interval.

RESULTS

Patients and tumor characteristics for the whole group were presented in Table (1). The characteristics of pediatric and adult groups were also listed in Table (2).

In the adult group, there were 27 male (66%) and 14 female patients. Their mean age was 52±16 years (range 20-81 years). Out of this group, 12 (29%) patients presented with recurrent lesions while the remaining 29 (71%) were first treated in our surgical department as primary presentation. Tumor mean size was 20±6 cm (range 8-31 cm) with a median value of 20 cm. Twenty patients (49%) had tumors < 20 cm in its maximum dimension. Liposarcoma was the most frequent pathology (37%), followed by lieomyosarcoma 15% and peripheral neuro-ectodermal tumor (PNET 12%). Twenty seven (66%) and 14 (34%) patients had low and high-grade lesions, respectively.

In the pediatric group, there were 8 male (42%) and 11 female patients (58%). Their mean age was 5±4 years (ranged from 1-18 years). Out of this group, only 3 patients (16%) presented with recurrent lesions while the remaining 16 (84%) had primary presentation. Tumor mean size was 15±6 cm^2 (ranged from 5-25 cm^2) with a median value of 14 cm^2. Twelve patients (63%) had tumors < 15 cm in its maximum dimension. Only one patient had a Rhabdomyosarcoma tumor and the remaining 18 patients had Peripheral neuro-ectodermal tumor (PNET). Nine (47%) and 10 (53%) patients had low and high-grade lesions, respectively.

Table (3) listed the treatment characteristics for both pediatric and adult groups. Complete gross resection had been achieved in 28/41 (68%) and 12/19 (63%) patients in the adult and pediatric groups, respectively. Visceral resection was not always accompanied with complete resection. Visceral resection was performed in 20 (49%) and 8 (42%) patients in the adult and pediatric groups, respectively. Out of those patients, gross residual disease was left behind at the tumor bed in 8 (40%) and 6 (75%) patients, respectively. On the other hand, the whole tumor was grossly resected without visceral resection in 16/21 (76%) and 10/11 (91%) in the adult and pediatric groups, respectively.

Out of the 41 adult patients, 11 cases (27%) received no adjuvant treatment. Nineteen patients (46%) received chemotherapy alone, 6 patients (15%) had radiotherapy alone and 5 patients (12%) had both radio-chemotherapy as their adjuvant postoperative treatment. The corresponding values for the pediatric group were 2 patients (11%) with no adjuvant treatment, 13 (67%) with chemotherapy alone, 2 (11%) had radiotherapy alone and the remaining 2 patients (11%) had both radio-chemotherapy (Table 3).

Survival analysis:

For the whole group the overall survival was 7% and DFS was 38% at 18 months (Figs. 1 & 2). The following factors affected overall survival significantly (Table 4): presentation size of tumor, grade, surgical resection, visceral resection and adjuvant radiotherapy. Age groups and gender affected DFS significantly in addition to the previously mentioned factors (Table 4). Female patients had a statistically significant better DFS rate (56% compared to 26% for the males, $p = 0.047$). Also, there was a statistically significant difference between pediatric and adult groups for the DFS rate, 58% and 29%, respectively ($p = 0.037$). This was not reflected in the overall survival with both groups since 18-month overall survival rate was 73% in pediatric group and 65% in adults ($p = 0.684$).

Twenty-nine patients (71%), out of the 41 in the adult group, had treatment failure in the form of local relapse, 12 of them experienced distant metastases as well. In the pediatric group, 8/19 patients (42%) had local relapse, 5 of them had distant metastases as well (Tables 7 & 8).

On univariate analysis, most of the factors suggested to affect prognosis had a statistical significance on both DFS and overall survival for both groups as shown in Tables (7 & 8). In pediatric group, tumor size < 15 cm^2, low-grade pathology and complete resection had better overall survival as well as DFS. However, the

effect of type of presentation, adjuvant postoperative radiotherapy or chemotherapy can't be assessed owing to the small number of cases in each category.

In adults group, age < 50 years, primary presentation, tumor size < 20 cm^2, low-grade pathology, complete resection and the use of adjuvant postoperative radiotherapy had better overall survival as well as DFS.

Visceral resection showed a negative effect on both survival rates for both groups. For the pediatric group, the difference was statistically significant, with overall survival 50% and DFS of 25% in cases subjected to visceral resection, compared to 91% and 82% for those with no visceral resection, $p = 0.002$ and 0.012, respectively (Table 7). However, for the adult group, the difference was statistically insignificant for both survival rates, $p = 0.237$ and 0.814 for overall survival and DFS, respectively (Table 8).

All the patients who received adjuvant PORT (11 adult and 4 pediatric groups) survived for the whole 18 months. Twenty out of the 45 patients (44%) who did not receive postoperative radiotherapy died of the disease within the 18 months ($p < 0.001$). The DFS rates were 67% and 29% for patients with and without postoperative radiotherapy, respectively ($p = 0.006$) (Table 4).

Multivariate analysis:

For the whole group, surgical resection and type of presentation were found to have a significant effect on overall survival ($p < 0.001$ and 0.032, respectively; with Odds ratio 25.83 and 2.83, respectively) (Table 5).

DFS was significantly affected by surgical resection and age groups ($p < 0.001$ and 0.007, respectively; with Odds ratio 8.54 and 2.66, respectively) (Table 6).

In the adults group, surgical resection was found to have a significant effect on overall survival ($p < 0.001$ with Odds ratio 72.71). Also, surgical resection affected the DFS ($p < 0.001$ with Odds ratio 6.11).

In the pediatric group, no factor proved to have a significant effect on overall survival. However, surgical resection affected the DFS ($p = 0.003$ with Odds ratio 26.57).

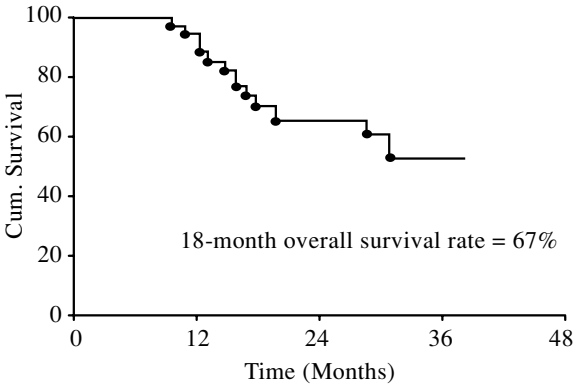

Fig. (1): Overall survival rate for the whole group.

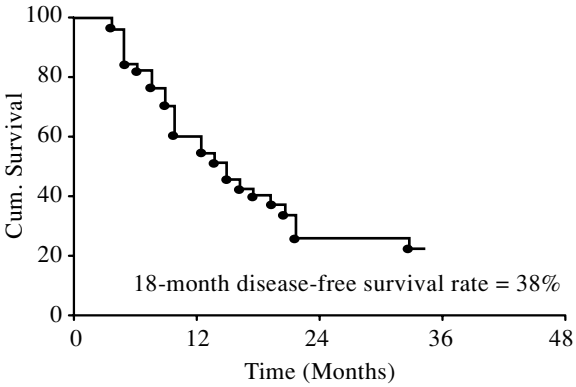

Fig. (2): Disease-free survival rate for the whole group.

Table (1): Patient and tumor characteristics of the whole study group.

Patient characteristics	Whole group (60)	
	No.	%
Age (years):		
Median (range)	37 (1-81)	
Mean ± SD	37±26	
Adult	41	68
Pediatric	19	32
Gender:		
Male	35	58
Female	25	42
Tumor characteristics:		
Presentation:		
Primary	45	75
Recurrent	15	25
Size (cm)		
Median (range)	18 (5-31)	
Mean ± SD	18±7	
< 20	27	45
≥ 20	33	55
Pathological types:		
PNET	23	38
Liposarcoma	15	25
Lieomyosarcoma	6	10
Rhabdomyosarcoma	2	3
Others	14	24
Grade:		
Low	36	60
High	24	40

Table (2): Patient and tumor characteristics of adult and pediatric groups.

Patient characteristics		Adult group (41)			Pediatric group (19)	
		No.	%		No.	%
Age (years):		52 (20-81)			4 (1-18)	
Median (range)		52±16			5±4	
Mean ± SD						
	< 50	18	44	< 3	7	37
	≥ 50	23	56	≥ 3	12	63
Gender:						
Male		27	66		8	42
Female		14	34		11	58
Tumor characteristics:						
Presentation:						
Primary		29	71		16	84
Recurrent		12	29		3	16
Size (cm)						
Median (range)		20 (8-31)			14 (5-25)	
Mean ± SD		20±6			15±6	
	< 20	20	49	< 15	12	63
	≥ 20	21	51	≥ 15	7	37
Pathological types:						
PNET		5	12		18	95
Liposarcoma		15	37		0	0
Lieomyosarcoma		6	15		0	0
Rhabdomyosarcoma		1	2		1	5
Others		14	34		0	0
Grade:						
Low		27	66		9	47
High		14	34		10	53

Table (3): Treatment characteristics of the adult and pediatric groups.

	Adult group (41)		Pediatric group (19)	
	No.	%	No.	%
Extent of resection:				
Complete resection	28	68	12	63
Incomplete resection	13	32	7	37
Visceral resection:				
Yes	20	49	8	42
With complete resection	12*	60*	2	25
With incomplete resection	8*	40*	6	75
No	21	51	11	58
With complete resection	16#	76#	10	91
With incomplete resection	5#	23#	1	9
Adjuvant treatment:				
No	11	27	2	11
Chemotherapy alone	19	46	13	67
Radiotherapy alone	6	15	2	11
Both RTH + CTH	5	12	2	11

* Number of patient relative to the patients with visceral resection.
£ Number of patient relative to the patients without visceral resection.

Table (4): Overall survival and disease-free survival rates, for the all patients according to the patients, tumor and treatment factors.

	No.	18-month Overall survival rate	*p*-value	18-month Disease-free survival rate	*p*-value
All patients	60	67%		38%	
Age:					
Adults	41	65%		29%	
Pediatric	19	73%	0.684	58%	0.037
Gender:					
Male	25	67%		26%	
Female	35	68%	0.786	56%	0.047
Presentation:					
Primary	54	82%		47%	
Recurrent	15	27%	< 0.001	13%	< 0.001
Size:					
< 20 cm	33	93%		63%	
≥ 20 cm	27	36%	< 0.001	7%	< 0.001
Grade:					
Low grade	36	96%		58%	
High grade	24	28%	< 0.001	8%	< 0.001
Pathological types:					
PNET	23	56%		43%	
Liposarcoma	15	79%		47%	
Others	22	75%	0.286	27%	0.820
Surgical resection:					
Complete	40	97%		57%	
Partial	20	15%	< 0.001	0%	< 0.001
Visceral resection:					
Yes	28	53%		32%	
No	32	79%	0.006	44%	0.006
Adjuvant radiotherapy:					
Yes	15	100%		67%	
No	45	56%	0.001	29%	0.006
Adjuvant chemotherapy:					
Yes	39	63%		33%	
No	21	75%	0.174	48%	0.262

Table (5): Multivariate analysis of significant variables to overall survival for the whole group.

	B	SE	*p*-value	OR	95% Confidence interval of OR	
					Lower	Upper
Surgical resection	3.25	0.68	< 0.001	25.83	6.88	96.97
Presentation	1.04	0.49	0.032	2.83	1.09	7.33

Table (6): Multivariate analysis of significant variables to disease-free survival for the whole group.

	B	SE	*p*-value	OR	95% Confidence interval of OR	
					Lower	Upper
Surgical resection	2.14	0.39	< 0.001	8.54	3.92	18.62
Age group	0.98	0.36	0.007	2.66	1.31	5.39

B : Regression coefficient.
SE: Standard error.
OR: Odds ratio.

Table (7): Overall survival and disease-free survival rates, for the pediatric group, according to the patients, tumor and treatment factors.

	No.	18-month Overall survival rate	*p*-value	18-month Disease-free survival rate	*p*-value
All patients	19	73%		58%#	
Age:					
< 3 years	7	86%	0.107	86%	0.063
≥ 3 years	12	65%		42%	
Gender:					
Male	8	73%	0.912	50%	0.754
Female	11	73%		64%	
Presentation:					
Primary	16	65%	*	42%	*
Recurrent	3	0%		0%	
Size:					
< 15 cm	12	92%	0.004	83%	0.005
≥ 15 cm	7	43%		14%	
Grade:					
Low grade	9	100%	< 0.001	100%	0.001
High grade	10	47%		20%	
Surgical resection:					
Complete	12	100%	< 0.001	92%	< 0.001
Partial	7	29%		0%	
Visceral resection:					
Yes	8	50%	0.002	25%	0.012
No	11	91%		82%	
Adjuvant radiotherapy:					
Yes	4	100%	*	100%	*
No	15	65%		47%	
Adjuvant chemotherapy:					
Yes	15	65%	*	53%	*
No	4	100%		75%	

8 patients (42%) had local relapse, 5 of them had distant metastases as well.
* Comparison of survival can't be done owing to the small number of cases.

Table (8): Overall survival and disease-free survival rates, for the adult group, according to the patients, tumor and treatment factors.

	No.	18-month Overall survival rate	*p*-value	18-month Disease-free survival rate	*p*-value
All patients	41	65%		29%#	
Age:					
< 50 years	18	86%	0.016	55%	0.003
≥ 50 years	23	48%		9%	
Gender:					
Male	27	65%	0.685	19%	0.103
Female	14	64%		50%	
Presentation:					
Primary	29	83%	< 0.001	38%	< 0.001
Recurrent	12	25%		8%	
Size:					
< 20 cm	20	93%	< 0.001	50%	< 0.001
≥ 20 cm	21	37%		10%	
Grade:					
Low grade	27	95%	< 0.001	44%	< 0.001
High grade	14	14%		0%	
Pathological types:					
PNET	5	0%	*	0%	*
Liposarcoma	15	79%		47%	
Others	21	74%		24%	
Surgical resection:					
Complete	28	95%	< 0.001	43%	< 0.001
Partial	13	8%		0%	
Visceral resection:					
Yes	20	56%	0.237	34%	0.814
No	21	73%		24%	
Adjuvant radiotherapy:					
Yes	11	100%	< 0.001	55%	0.011
No	30	50%		20%	
Adjuvant chemotherapy:					
Yes	24	62%	0.232	20%	0.089
No	17	69%		41%	

29 patients (71%) relapsed locally, 12 of them had distant metastases as well.
* Comparison of survival can't be done owing to the small number of cases.

DISCUSSION

Interpretation of outcomes of retroperitoneal sarcomas should be performed with extreme care due to the inherent heterogeneity with respect to pathologic types, sites of involvement, local extent and rarity of cases. Studies characterizing long-term follow-up and patterns of recurrence are limited.

Very few reports concerned with retroperitoneal sarcoma, addressed the effect of age as a prognostic factor [3,8]. Our data showed that pediatric group of patients had a more favorable DFS compared to adult group, although this was not reflected on overall survival. For the adult group, our results agreed with that of Heslin et al. [8] who reported a better survival rate for the patients aged less than 50 years. Meanwhile, Bevilacqua, in his study, didn't show any effect for the age [3]. Retroperitoneal sarcomas were not studied within the pediatric age group in any study so far.

For the gender, although there was no effect within each age-group, our female patients, collectively, had a significantly better DFS rates compared to the males, 56% and 26%, respectively ($p = 0.047$). Several studies have addressed the effect of gender as a prognostic

factor in retroperitoneal sarcomas [2,6,8,11-14]. Youssef et al., in his report raised the hypothetical possibility that the growth of soft-tissue sarcoma may be regulated by sex hormones [14]. Similarly, Remmelink et al., documented distinct patterns of sensitivity for various sarcoma cell lines to different hormones and growth factors [12]. In fact, this could be an interesting topic for further study and may have therapeutic implications.

As regard tumor size, although some authors didn't present a significant value for the tumor size [2,3,6] others correlated the tumor resectability to the size [13]. In this study, big lesions (> 20 cm^2 for adult and > 15 cm^2 for pediatric patients) had a significant lower overall and DFS rates. Tumors with large size reflect a late stage and higher possibility of organ, nerve and bone invasion, with decreased chance for complete resection.

In our study, high-grade tumors had a significantly lower overall survival and DFS rate within each group. Most of the published reports proved grade as an independent factor for both overall survival and local control [3,6-8,13,15]. High-grade tumors are often associated with more locally advanced, unresectable, or metastatic disease [3,8,15].

For the treatment-related factors, almost all the reports had studied the effect of surgical margin status on survival. With the exception of one study [6], most have concluded that complete surgical excision was significantly associated with improved overall survival [3,7,8,11,13,15-17]. Our results support that observation, as all the patients with partial resection had local relapse and died of the disease by 18 months in both adults and children. The resection margin status was a significant predictor on both univariate and multivariate analyses done by Catton et al. [2]. He reported a 5- and 10-year rate of loco-regional control of 50% and 18%, respectively, in patients who had complete excision. These rates were only 14% and 5% in patients with incomplete excision.

Radiotherapy (RT) arose as an important adjuvant treatment for soft tissue sarcoma in the view of the high probability for local recurrence that decreased long-term survival. The role of adjuvant RT in patients with retroperitoneal sarcoma is not as well established as in extremity sarcoma [2,8,16-17]. Several technical and radiobiological factors limit the effective use of RT in retroperitoneal sarcoma and may explain the controversial data in the literature about its effect. These include advanced stage at diagnosis. A relatively high incidence of residual disease after surgical resection necessitated high radiation doses for local control. However, the presence of surrounding normal tissue (lung, small bowel, kidney and liver) with limited radiation tolerance and difficult delineation of the area to be treated were factors that added to the difficulties in applying PORT.

Intraoperative electron beam radiotherapy "IOERT" is one of the techniques that allow the radiation oncologist to deliver radiation with better accuracy and with proper shielding of normal organs, thus improving the therapeutic ratio. In 2 prospective small non-randomized trials, IOERT (range 12-15 Gy) was used postoperatively with EBRT (range 45-50.4 Gy) [16,18]. The improvement in local control was significant in the intraoperative RT arm in both studies. The authors in both studies concluded a better local control for primary disease with this approach. However, they did not present an improvement in distant metastasis and treatment of recurrent disease.

Brachytherapy represents an effective means of enhancing the therapeutic ratio, offering both biologic and dosimetric advantage in the treatment of patients with soft tissue sarcoma. However, the treatment approach used depends upon the institution, expertise physician and the clinical situation. In their final report, the American Brachytherapy Society published their recommendations for brachytherapy of soft tissue sarcomas [19]. They considered brachytherapy used alone or in combination with external beam irradiation an established means of safely providing adjuvant local treatment after resection for soft tissue sarcomas both in adults and in children. Brachytherapy options included low dose rate techniques with iridium 192 or iodine 125, fractionated high dose rate brachytherapy, or intraoperative high dose rate therapy. Recommendations are made for patient selection, techniques, dose rates and dosages.

In conclusion, the results of our study demonstrate the paramount importance of local control and complete surgical resection in the

management of soft-tissue sarcoma of the retroperitoneum and deep trunk. The oncologist should offer his patient the best chance to achieve local control. In our opinion, this could be through gross total resection and the addition of adjuvant radiotherapy. Megavoltage external beam radiotherapy is the currently used method. However, we think that brachytherapy boost dose would be of help to offer a better tumor control.

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