Retroperitoneal Sarcoma: Is It Time to Change the Surgical Policy?

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ABSTRACT

Background. Complete tumor resection is the mainstay of treatment for retroperitoneal sarcoma (RPS), but the size and quality of surgical margins for radical resection in RPS are unknown. They are believed to be pushing tumors, but recently, aggressive surgical policies leading to multivisceral resection have seemed to suggest better local control compared with simple tumor resection. We analyzed a single-institution series of RPS to provide information useful to surgical decision-making.

Methods. From 1996 to 2008, 77 patients referred to our institution underwent surgery for primary RPS. Thirty tumors were classified as liposarcoma, and 20 as leiomyosarcoma. Potential prognostic factors were tested retrospectively. Number and pathologic status of resected organs were assessed.

Results. 151 organs were resected. Ninety-two were involved by the tumor (60.9%). Liposarcoma involved 48 of 77 organs resected for this histotype (62.3%). Infiltrative pattern was observed in 39/92 organs, and expansive pattern in 53/92 viscera. The infiltrative pattern was more often observed in leiomyosarcoma and non-lipogenic tumors. The expansive pattern was more often observed in

liposarcoma. Psoas was the organ most often involved by infiltrative pattern (12/14); the kidney was the organ most often involved by expansive pattern (19/28). 80% of patients had at least one viscera infiltrated by the tumor.

Conclusions. This series, in which an aggressive surgical policy was adopted along with extensive pathologic sampling, shows that RPS has a high rate of viscera infiltration. This growth pattern is characteristic of well-differentiated liposarcoma too. These pathologic data should be considered when planning surgical strategy.

Retroperitoneal soft tissue sarcomas (RPS) are rare tumors, with expected incidence of less than 1 case per 100,000 inhabitants/year.¹ Liposarcoma is the most common histotype.² Long-term prognosis is poor.^{3–5} Surgery is the mainstay of treatment; nevertheless, the large size of these tumors and their proximity to vital structures and visceral organs make the surgical procedure complex and challenging. The best surgical approach is not yet established.^{6–8} They are believed to be pushing tumors, and their simple resection along with surrounding viscera when directly infiltrated is the standard treatment. Nevertheless, an aggressive surgical policy proposing associated multivisceral resections, including the neoplastic mass, and with wide surgical margins around the tumor, has recently been proposed and has been adopted in several centers across Europe.^{7,9,10} However, few data are currently available on which to base definitive recommendations. Multimodality combined treatments of chemotherapy and radiotherapy plus surgery are under investigation, but definitive evidence of their efficacy is unavailable so far.^{11–16} Furthermore, the clinical pattern, and consequently the

treatment, can be very different at diagnosis and after one or more recurrences.⁵

The aim of this study is to analyze a large single-institution series of primary RPS to provide information on the clinical and histological behavior of the disease that could help surgical decision-making.

PATIENTS AND METHODS

The present series was selected from 1,310 consecutive soft tissue sarcoma (STS) patients surgically treated with curative intent at the IRCCS, Istituto Clinico Humanitas, Italy, between December 1996 and December 2008. Among these, we surgically treated 150 cases of RPS, including 77 primary and 73 referred after recurrence. Only primary tumors are the subject of the present analysis. Uterine and gastrointestinal sarcoma were not included.

Periodical follow-up (FU) comprised physical examination, abdominal computed tomography (CT) scan or magnetic resonance imaging (MRI) and chest X-ray, being ordinarily planned at 4-month intervals for 2 years after surgery, twice a year for the subsequent 3 years, and once a year thereafter. Our policy is to follow patients up to 10 years after their most recent operation, after which further follow-up is transferred to the local primary physician.

All patients included in the study underwent surgery with curative intent. Our surgical policy is to remove the tumor with wide healthy margins. The practical application of this approach changed over time, leading, in latter years, to associated multivisceral resection in all primary cases, even when gross visceral infiltration by the tumor mass was not recognized. The term “simple resection” is used herein when the tumor was removed alone or with omentum or adjacent peritoneum. “Associated visceral resection” is used when the tumor was resected with at least one adjacent organ, except omentum or peritoneum. Surgical resection was classified as macroscopically complete (R0 or R1) or not (R2). R2 resection applies when either there was tumor rupture or less than 5% of the whole tumor mass was left. Laparotomy and surgical debulking are not included in the present series. Common Terminology Criteria for Adverse Events was used to classify postoperative complications.¹⁷ All complementary treatments were administered on the basis of decisions taken by the multidisciplinary institutional Sarcoma Board. Chemotherapy was given according to the standard regimens used at the time or within experimental phase II trials. External-beam radiation therapy was given at doses ranging from 41.4 to 66 Grays (Gy) (median 50.4 Gy). Chemotherapy was used both preoperatively and postoperatively, mainly in young people affected by high-grade RPS or grade 2–3 multifocal

tumors. Radiotherapy was administrated mainly in the preoperative setting in patients affected by tumors localized in critical anatomic site (i.e., close to the spine).

Pathologic Evaluation of Resected Viscera

For examination of extension of tumor, multiple serial sections of the mass and of involved viscera were performed. Specific sites every 1–2 cm of tumor borders with macroscopic impression of viscera infiltration were sampled. At the same time, serial sampling was also performed randomly around viscera, also in cases in which tumor invasion was not macroscopically documented. Sampling sites depend on case and type of resection; where possible, perirenal fat adjacent to cortical parenchyma, periadrenal adipose tissue, pericolic fat in proximity to the tumoral mass, and all suspect areas of psoas muscle were serially sampled.

We subdivided visceral involvement by tumor into two major types: the *infiltrative* type, in which the visceral structure is not embedded by the tumor but there is clear, either focal or diffuse, infiltration by nests or single cells of normal renal cortex, hilar vessels, tunica muscularis of the bowel and the ureter, psoas muscle, pancreas, adrenal gland, liver, spleen, etc.; and the *pushing* type (expansive), in which the viscerum is totally or partially (three dimensions) embedded into tumor with ill-defined borders, without microscopic evidence of infiltration (i.e., invasion of perirenal adipose tissue without infiltration of the cortex by well-differentiated liposarcoma), often without normal fat tissue between tumor and viscera.

The repeated pathologic examinations were carried out by the same soft tissue pathologist. Tumors were classified according to the World Health Organization (WHO) classification of STS. Tumor grade was assessed according to the three-tier Fédération Nationale des Centres de Lutte Contre le Cancer (FNCLCC) criteria, which take into account tumor differentiation (D), mitotic index (M), and presence of necrosis (N). Grading of tumors which received preoperatively either chemotherapy or radiation therapy was assessed based on preoperative biopsy.

Statistical Analysis

Data are presented as number and percentage, or median and range, where appropriate. Overall and local disease-free survival (LDFS) were calculated by Kaplan–Meier method, from date of first surgery to date of last contact. For patients who underwent R2 surgical resection we analyzed progression-free survival (PFS). Differences between groups were tested using a Cox regression model. Survival data are presented as odds ratio (OR) and confidence interval (CI).

All analyses were carried out using Stata10 software (www.stata.com).

RESULTS

Patient and tumor characteristics are presented in Table 1. Thirty tumors were classified as liposarcoma, and 20 as leiomyosarcoma. The other types were polymorphic sarcoma not otherwise specified (NOS), synovial sarcoma, desmoplastic small round cell tumor, solitary fibrous tumor or myxofibrosarcoma. Twenty-five cases were classified as grade 1, 21 as grade 2, and 31 as grade 3 according to the FNCLCC criteria. Among the liposarcoma group, 14 were well differentiated (WD) and 16 were dedifferentiated (DD). Five patients (6%) had multifocal disease at diagnosis. Beside surgical resection, 27 patients (35%) were treated by chemotherapy. Twenty-three patients (29%) received radiotherapy; among these, eight patients received both chemotherapy and radiotherapy preoperatively within an Italian Sarcoma Group phase II trial of concurrent preoperative chemotherapy and radiotherapy in retroperitoneal soft tissue sarcoma.

Grade 3–5 postoperative complications were recorded in 15% cases. Among these, three patients required further operation (4%) and three (4%) had hospital stay longer than 1 month. One surgically related death was recorded (1.3%). Two of these patients had only simple resection as the primary surgical procedure: one patient required a second operation for bleeding and the other one nephrectomy for urinary fistula after failure of endoscopic ureteral stenting. This patient had residual liposarcoma in the kidney resected for the complication.

TABLE 1 Main clinicopathological characteristic of 77 patients affected by primary RPS

	Primary
N	77
Age at diagnosis median (range), years	56.5 (20–83)
Sex (male)	42 (54.55%)
Grading (FNCLCC)	
1	25 (32.46%)
2	21 (27.27%)
3	31 (40.25%)
Histology	
Liposarcoma	30 (38.96%)
Leiomyosarcoma	20 (25.97%)
Other	27 (35.06%)
Tumor size, median (range), cm	17 (3–91)
Chemotherapy	27 (35.06%)
Radiotherapy	23 (29.87%)
Complete surgery (R0–R1)	68 (88.31%)

Fifty patients had at least one total or partial visceral resection en bloc with the tumor. Details of resected organs and type of infiltration are reported in Table 2. Data for patients who had only omentum or peritoneum resection are not listed in the table; these cases were classified as simple resection.

One-hundred fifty-one organs were resected (1.9/patient), 92 of which were involved by the tumor (60.9%). Liposarcoma involved 48 out of 77 viscera resected for this histotype (62.3%); leiomyosarcoma involved 20 organs out of 28 resected for this histotype (71.4%). Eighteen organs were involved by well-differentiated liposarcoma out of 37 resected for low-grade liposarcoma (48.6%). Thirty organs were involved by DD liposarcoma (75%), 25 by the DD component, and 5 by the WD component.

80% of patients had at least one viscera infiltrated by the tumor. Infiltrative growth pattern was observed in 39/92 organs; expansive growth pattern was observed in 53/92 cases (Fig. 1a–d). The infiltrative pattern was more often observed in leiomyosarcoma and non-lipogenic tumors (polymorphic sarcoma NOS, myxofibrosarcoma). The expansive pattern was more often observed in liposarcoma. Psoas was the organ most often involved by infiltrative pattern (12/14); the kidney was the organ most often involved by expansive pattern (19/28). Microscopic positive margins were recorded in 19/77 (25%) cases; no statistical differences were noticed between patients who had simple resection and patients who had associated viscera resection.

Five-year LDFS and OS were 52% and 73%, respectively (Fig. 2a, b). Median follow-up was 17.5 months. Median survival was not reached. Forty-five patients were alive and disease free at the end of follow-up; 15 were dead (9 of local relapse, 4 of distant metastases, 1 of surgical complications, 1 of other causes). No patients were lost to follow-up.

No differences were noticed according to surgical approach (simple resection versus associated viscera resection). Prognostic factors for LDFS and OS are reported in Table 3. Tumor diameter was the only statistically significant prognostic factor for LDFS. Patients who received R2 resection had poorer local control, although this was not statistically significant due to the small number of patients ($p = 0.068$). A slight trend toward worse local control was observed for liposarcoma compared with leiomyosarcoma, but overall survival was similar due to the lower incidence of distant metastases in the liposarcoma subgroup. A negative prognostic trend for OS was recognized for males and for high-grade tumors. Grade was close to reaching statistical significance as a prognostic factor for local control.

Twelve patients had a second surgical procedure after the first recurrence. One-year and 2-year LDFS were 25% and 8%, respectively.

TABLE 2 Viscera resected and microscopic pattern of tumor invasion (infiltrating versus pushing)

Resected viscera	Number	Infiltrative involvement histotypes			Pushing involvement histotypes			Total involved
		Leio	Lipo	Other types	Leio	Lipo	Other types	
Kidney	28	2		1	4	12	3	22/28 (78.5%)
Ureter	24	2		1	1	6	1	11/24 (45.8%)
Adrenal	20	1			2	7		10/20 (50%)
Colon	20	1	5	1	1	4	1	13/20 (65%)
Psoas	14	3	5	4		2		14/14 (100%)
Vessels	7			2			1	3/7 (42.8%)
Ileum	7					3	1	4/7 (57.1%)
Liver	5		1	2				3/5 (60%)
Spleen	5			1	1	1		3/5 (60%)
Bone	4	1		2				3/4 (75%)
Pancreas	4		1		1	1		3/4 (75%)
Omentum	3			2				2/3 (66%)
Diaphragm	1							0/1 (0%)
Uterus	1							0/1 (0%)
Other ^a	8			1				1/8 (12.5%)
Total	163	10	12	17	10	36	7	92/151 (60.9%)

Other types: polymorphic sarcoma NOS, synovial sarcoma, desmoplastic small round cell tumor, solitary fibrous tumor, myxofibrosarcoma

^a Other: gallbladder (4 cases), ovary (3 cases), seminal vesicle (1 case)

FIG. 1 Visceral involvement with infiltrative pattern of muscle fibers of psoas (a) and small bowel wall (b) by a well-differentiated liposarcoma. Pushing pattern of growth of a sclerosing and lipoma-like liposarcoma (c, d). In the case in (c) the tumor closely and circumferentially involved the ureter, while in the case in (d) the

muscular wall of the colon is in tight junction to the neoplastic mass without evidence of any microscopic focus of infiltration. (a) H/E, original magnification $\times 200$; (b) H/E, original magnification $\times 100$; (c) H/E, original magnification $\times 100$; (d) H/E, original magnification $\times 200$)

FIG. 2 Five-year LDFS (a) and OS (b) of 77 patients affected by primary RPS. Number of patients at risk (relapsed/dead) is shown for each year. Brighter lines show the confidence interval

TABLE 3 Results from Cox models for 77 patients affected by primary RPS

	LDFS-PFS			OS		
	HR	CI	p	HR	CI	p
Age at diagnosis	0.988	0.963–1.014	0.356	0.978	0.945–1.012	0.211
Sex (male)	1.621	0.716–3.667	0.246	2.997	0.914–9.832	0.070
Grading (FNCLCC)						
1	1			1		
2	3.205	0.865–11.876	0.081	3.261	0.338–31.46	0.307
3	3.250	0.902–11.708	0.071	7.099	0.896–56.27	0.064
Histology						
Liposarcoma	1			1		
Leiomyosarcoma	0.501	0.157–1.602	0.244	1.074	0.240–4.803	0.925
Other	1.015	0.422–2.441	0.973	1.456	0.410–5.169	0.561
Tumor diameter	1.028	1.008–1.048	0.006	0.991	0.947–1.038	0.701
Chemotherapy	1.057	0.469–2.381	0.893	0.451	0.124–1.642	0.227
Radiotherapy	1.573	0.691–3.579	0.280	1.743	0.583–5.213	0.320
Surgery (R2)	2.512	0.936–6.743	0.068	2.670	0.733–9.727	0.136
Surgery (simple)	0.989	0.490–3.578	0.355	0.920	0.205–5.323	0.927
Multifocality	1.647	0.490–5.536	0.419	0.820	0.106–6.329	0.849

HR hazard ratio

DISCUSSION

In the present series we analyzed 77 patients who presented and were surgically treated at our institution at first diagnosis. Our pathologic review shows associated organs resected adjacent to the tumor were involved in most cases. Many cases were well-differentiated liposarcoma. These pathologic data are important because sarcoma, and especially liposarcoma, are too often believed by surgeons to be masses that press but do not invade and are, consequently, treated by simple resection. The pathologic infiltrative behavior of liposarcoma is difficult to recognize because well-differentiated “lipoma-like” areas of the tumor are similar to retroperitoneal normal fat. Nevertheless, the high local recurrence rate of liposarcoma proves that it has local malignant behavior.⁵ Both in our series and in the

literature, liposarcoma has worse local control than leiomyosarcoma.^{3,6} Long-term survival is similar due to the low incidence of distant metastases in the liposarcoma subgroup.

Our data show that, when multivisceral resection is performed along with extensive sampling, resected viscera are infiltrated in most cases, and well-differentiated liposarcoma is not an exception to this rule. For instance, it is worth noting the high rate of psoas involvement by the tumor (100%). These data suggest that RPS should be treated as an extremity sarcoma, with surgical resection including a wide envelope of normal tissue surrounding the tumor to include any tumor satellites and skip metastases. Nevertheless, this approach is more difficult to translate into clinical guidelines than for extremity and superficial trunk sarcoma. In limb sarcoma, wide surgical resection of

the tumor along with the muscle around it gives good local control and reduces incidence of local recurrence compared with simple resection of the tumor.^{18–20} In the abdominal and retroperitoneal space, it is not so easy to take wide and negative margins when resecting viscera adjacent to the tumor. Furthermore, the impact of such a policy in terms of morbidity is very different. The main argument against a policy of liberal multivisceral resection en bloc with the tumor is that the risk of surgical morbidity and mortality outweighs the clinical benefit in terms of survival and disease-free survival.^{6,8} The second argument against unnecessary visceral resection is that wide surgical margins are difficult to achieve in the retroperitoneal space, even when multivisceral resection is performed. This is due to the large size of the tumor masses and their proximity to vital structures that cannot be resected. The practical consequence is that there are anatomic sites where surgery can easily obtain wide negative margins, whereas there are critical anatomic sites (i.e., spine, pancreas, mesenteric artery and vein, etc.) where surgery is either definitely marginal, according to Enneking classification, or highly risky.⁸

On the other hand, surgical and anesthesiological techniques have improved in recent years and increasingly allow us to perform complex surgical procedures safely. Radiotherapy techniques have improved too, and can be combined with surgical treatment, especially at critical and marginal sites. The purpose of an aggressive multivisceral surgical policy is to reduce tumor handling and improve the quality of surgical margins. This approach would reduce the incidence of multifocal recurrence and is easier to integrate with radiotherapy, which could be administrated only for critical marginal sites. Two recent retrospective reviews of two series of retroperitoneal sarcoma reported by Gronchi and Bonvalot suggest that local disease control is improved when the tumor is removed en bloc with surrounding viscera, compared with simple tumor resection.^{7,9,21} Furthermore, Bonvalot found residual tumor in 80% of patients who underwent re-excision of the tumor bed after simple complete resection of the neoplasm. Pathologic status of removed viscera was not reported. In our series, 80% of patients had at least one viscera infiltrated by the tumor: among 151 organs resected, 61% were directly infiltrated on pathologic assessment. We have shown for the first time that pathologic data offer a strong rationale for a surgical policy oriented towards application of wide surgical margins to tumor sites, including those in the abdominal and retroperitoneal space. However, we cannot reach any conclusion regarding the impact of en bloc resection in terms of local control of adjacent viscera in our series, because we retrieved a heterogeneous sample and many of our patients underwent simple resection,

especially in the first years of the study. Local disease-free survival in our series is similar to LDFS obtained by other groups that treated heterogeneous series.^{2,3} If we compare our results with results reported by the French Association of Surgery, our patients had favorable outcome compared with patients who received organ resections because of clear infiltration, and similar outcome to patients who received simple resection.⁹ These data can be understood if we consider that these two groups from the French Association of Surgery series carry negative and positive selection bias, respectively. In fact, indolent tumors can be removed by simple resection, and they have better prognosis per se; instead, aggressive tumors often clearly infiltrate adjacent organs and cannot be resected alone, even if surgeon preference is for conservative approaches. These aggressive tumors are usually characterized by negative prognostic factors and poor prognosis.

LDFS of our patients was inferior to LDFS of patients treated by frontline, systematic multivisceral resections by Bonvalot and Gronchi. Those patients received multivisceral resection whether or not the tumor clearly infiltrated surrounding viscera. Although comparisons between historical controls and different series are prone to bias, this difference in terms of LDFS could be due to the more aggressive approach adopted in those series.

Surgical morbidity was at acceptable levels, being within the range of morbidity reported for major surgical procedures for malignant disease.^{5,22} It is worth noting that many of our patients also received preoperative chemotherapy or radiotherapy, or both, potentially increasing surgically morbidity.

Taken together, these data support the efforts of surgeons to improve the quality of surgery through en bloc resection of adjacent viscera. Unfortunately, it is not realistic to suggest a prospective randomized study to clarify the role of the multivisceral surgical approach, due to the rarity and heterogeneity of the disease. However, larger prospective analyses are necessary to provide more information about the efficacy and morbidity of such an approach.

CONCLUSIONS

Based on this series, in which an aggressive surgical policy was adopted along with extensive sampling of the specimen by expert soft tissue pathologists, we have shown that, despite their apparent gross pushing growth pattern, RPS has a high rate of visceral infiltration. Furthermore, we underline that the infiltrative growth pattern is characteristic not only of high-grade RPS, but also of well-differentiated liposarcoma. These histopathological data should be considered when planning surgical strategy.

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