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Prognostic factors for the primary and secondary retroperitoneal sarcomas. Impact on the therapeutic approach

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Rezumat

Factori prognostici pentru sarcoamele retroperitoneale primare și secundare. Impactul asupra abordării terapeutice

Există o cunoaștere prea limitată privind sarcoamele retroperitoneale, dar persistă în schimb multe controverse. Obiectivul acestui studiu a fost definirea trăsăturilor comune și distincte ale sarcoamelor retroperitoneale primitive și secundare în termeni de prezentare, prognostic și abordare terapeutică în vederea îmbunătățirii managementului acestor tumori. Impactul implicării vasculare a fost evaluat pentru cele două grupe de pacienți.

Pacienți și metode: Am realizat un studiu retrospectiv și prospectiv pe un grup de 34 de pacienți diagnosticați cu sarcoame retroperitoneale primitive și secundare.

Rezultate: Noi am găsit că sarcoamele retroperitoneale primitive și secundare prezintă multe trăsături comune, dar și diferențiale din punct de vedere al manifestării, predictorilor supraviețuirii și tratamentului.

Discuții: Implicarea vasculară este unul dintre cei mai importanți predictori pentru o supraviețuire redusă în cazul pacienților cu sarcoame retroperitoneale primitive, deoarece împiedică radicalitatea. În acest grup, radicalitatea este factorul major de prognostic pentru o supraviețuire mai îndelungată. În schimb, supraviețuirea în sarcoamele retroperitoneale secundare pare a fi mai puțin dependentă de radicalitatea tratamentului și răspunde la tratamente complementare.

Cuvinte cheie: retroperitoneal, sarcoame, supraviețuire, sarcoame retroperitoneale primitive, sarcoame retroperitoneale secundare, implicare vasculară, prognostic

Abstract

Background: There is little knowledge on retroperitoneal sarcoma, but there are many controversies. The objective of the current study was to define the common and distinctive features of primary and secondary retroperitoneal sarcomas in terms of presentation, prognostic and therapeutic approach to improve the current management of these tumors. Vascular involvement impact was assesed in the two sets of patients.

Patients and methods: We have performed a retrospective and prospective study on a group of 34 patients diagnosed with primary and secondary retroperitoneal sarcomas.

Results: We have found that primary and secondary retroperitoneal sarcomas have many common features, but hold distinctive aspects in terms of manifestation, predictors of survival and treatment.

Conclusions: Vascular involvement is one of the most important predictors of poor survival in primary retroperitoneal sarcoma patients, because it often limits radicality. In this group, radicality is a major prognostic factor for a higher survival. Instead, secondary retroperitoneal sarcomas appear to be less dependent on the radicality of the treatment and their survival can be increased by complementary treatments.

Key words: primary retroperitoneal sarcoma, secondary retroperitoneal sarcoma, vascular involvement, survival, prognostic

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Introduction

Soft tissue sarcomas are very rare tumors, of mesenchymal origin, accounting for 1% to 1.5% of all cancers (1). In this uncommon group of tumors, sarcomas localized in the retroperitoneum are even rarer, representing 15-20% of all soft-tissue sarcomas. They are associated with a poor prognosis, due to the advanced tumor stage at the presentation of the patient, with a low rate of curative surgical interventions, 36-58% overall 5-year survival rate, and high loco-regional recurrence rate responsible for death in the majority of cases (75% of sarcoma-related rates) (2,3). Retroperitoneal sarcomas have an insidious growth, with late, discrete, unspecific symptoms, the diagnosis being often made when the tumor has reached big, even gigantic dimensions, with direct and indirect involvement of important retroperitoneal and abdominal organs and blood vessels (4). Also, 10 to 20% of patients have distant metastases at the initial presentation to the hospital, regional lymph node involvement being uncommon (5). Retroperitoneal sarcomas represent a heterogeneous group of tumors, the most frequent histopathological types being liposarcomas (50% of all retroperitoneal sarcomas), followed by leiomyosarcomas (17-26%), malignant fibrous histiocytoma (11%) and other types. Well-differentiated liposarcoma appears to be associated with the most favourable prognosis of all tumor types. Most retroperitoneal sarcomas are of intermediate or high grade. The only proven efficient treatment is aggressive, radical surgical resection, with negative surgical margins, frequently requiring multivisceral and multivascular resections. The extent of aggressiveness in the resection of tumor-related tissues is still subject of debate, some authors advocating for a compartment surgery (6-8). The radicality of the surgery is considered to be the most important prognostic factor, many authors being unable to detect other determinants in the prognosis of these patients (1,9). However, the important tumor volume at the moment of surgery, the extended degree of nearby organ and blood-vessel involvement, the difficult surgical access into the retroperitoneal space, that has no specific anatomic boundaries, frequently determine microscopic or macroscopic residual disease after the surgical intervention (2). There are still controversies regarding the efficacy of adding adjuvant or neoadjuvant chemo- and radiotherapy to such patients. The rarity of these tumors in general and of the various histopathologic types, the lack of randomized trials regarding different forms of therapies, the different views of medical centers specialized in sarcoma treatment explain the deficits in our knowledge regarding retroperitoneal sarcomas and the necessity of a generalization and standardization in the management of retroperitoneal sarcomas (3,10-13). The aim of the current study was to analyse the outcome of surgical and complementary treatment in a group of patients diagnosed with retroperitoneal sarcomas, to define some of the characteristics of these tumors, with a comparison between primary and secondary retroperitoneal sarcomas.

Patients and Methods

A both retrospective and prospective study was performed on 34 patients diagnosed with primary or secondary retroperitoneal sarcoma in our Surgical Clinic, from 1999 to 2011. The retrospective period of the study extended from 1999 to 2008 and the prospective from 2009 to 2011. Data were obtained from patient medical records from the initial presentation and the regular follow-ups in our Institute. All patients were adults and exclusion citeria were all secondary retroperitoneal sarcomas keeping strictly of digestive organs (pancreatic, gastrointestinal), with no extension outside the organ into the retroperitoneal space. Inclusion ciriteria: all primary retroperitoneal sarcomas and secondary sarcomas of kidney, adrenal gland, involving the ureter, extensions of primary digestive organs into the retroperitoneum, all metastases of various cancers located in the retroperitoneum. Studied variables were related to the: patient (age, sex comorbidities, general health state at the initial evaluation, presenting symptoms and their duration) and tumor characteristics (tumor dimension, histopathologic type, grading), degree of vascular and visceral tumor involvement, type of surgical treatment, perioperative complications, type of complementary treatments, results of surgery, locoregional recurrence (free-disease period, number of recurrences, their management), metastases, follow-up of the patients.

Statistical analysis was performed with Excel and EpiInfo software. Overall 5-year survival of all operated patients and 5-year free-recurrence and free-disease survival rates were estimated using the Kaplan-Meier method. Cox regression model was helpful in determining predictors of recurrence-free disease survival and higher overall survival rates. In the follow-up and analysis of recurrence rates and predictors only the patients that were radically operated were included. A significance level of 0.05 was considered throughout the statistical analysis.

Results

34 patients diagnosed with primary and secondary retroperitoneal sarcoma were analysed. Only 32 patients were operated and 2 patients refused the surgical intervention, requiring imediate release from the hospital and were lost from the follow-up. The mean follow-up of the operated patients was of 1249 days (41.64 months), with a median of 1186.5 days. The average age of the operated patients was of 50.81 years, the median age being of 55.5 years. There were 21 female patients (65.625% of the operated patients) and 11 male patients (34.375% of the operated patients), the female/male ratio being of 1.9/1. Primary retroperitoneal sarcomas represented 59.375% (19 patients) and secondary sarcoma accounted for 40.625% (13 patients). The mean age of patients with primary sarcomas was of 54.42 years (median of 57 years), 63.2% being females and 36.8% males (female/male ratio of 1.71/1). In the group of patients with secondary retroperitoneal sarcomas the average age was of 45.53 years (median of 41 years), with a female/male ratio of 2.24/1, with an obvious predominance of

Table 1. *Secondary retroperitoneal sarcoma types in female and male patients*

Female patients			Male patients		
Initial tumor	**Frequency**	**Percent**	**Initial tumor**	**Frequency**	**Percent**
Gastrointestinal stromal tumor	0	0,0%	Gastrointestinal stromal tumor	2	50,0%
Mesenteric sarcoma	2	22,2%	Mesenteric sarcoma	0	0,0%
Epiplooic sarcoma	1	11,1%	Epiplooic sarcoma	0	0,0%
Extremity sarcoma	0	0,0%	Extremity sarcoma	1	25,0%
Kidney sarcoma	1	11,1%	Kidney sarcoma	1	25,0%
Uterine sarcoma	5	55,6%	Uterine sarcoma	0	0,0%
Total	9	100,0%	Total	4	100,0%

female patients diagnosed with secondary retroperitoneal sarcomas. 6 secondary sarcomas were localized in the retroperitoneum by direct invasion of a non-primary retroperitoneal tumor (3 from digestive structures - 2 gastrointestinal stromal tumors, 1 epiplooic sarcoma, and 3 from uterine sarcomas), 2 secondary sarcomas were metastases of previously apparently cured cancers (a uterine sarcoma and an extremity sarcoma), 2 were sarcomas of retroperitoneal organs (kidney), 2 were mesenteric sarcomas, 1 was localized into the retroperitoneum by direct invasion and metastazing. Female patients developed secondary retroperitoneal sarcomas especially by direct extension of uterine sarcomas into the retroperitoneum (leiomyosarcoma, adenosarcoma, endometrial stromal sarcoma) (55.6% of female secondary sarcomas); in 22.2% of cases female secondary sarcomas were represented by mesenteric sarcomas, kidney sarcomas (11.1%) and epiplooic sarcomas invading into the retroperitoneum (11.1%) being less frequent. No extremity sarcomas or gastrointestinal stromal tumors were involved in the development of secondary retroperitoneal sarcomas in female patients. Instead, in male patients, in 50% of cases gastrointestinal stromal tumors invading into the retroperitoneal space, kidney sarcomas or retroperitoneal metastases from extremity sarcomas were the mechanisms of development of secondary tumors in this anatomic space (*Table 1*).

The persistence of symptoms before patient presentation to the physician varied from one week to 4 years, but in most of the cases it was less than 3 months (*Table 2*). The most frequent symptom was pain, followed by an increase in abdominal dimensions and the perception of an abdominal mass. 53.1% of all patients (primary and secondary sarcomas) had tumor antecedents. The tumor was palpable in 75% of the cases at the initial medical inspection of the patient. Mean sarcoma diameter was 154.68 (mm), the median value was of 150 (mm), with extreme values of 60 and 400 (mm). There was a non-significant difference between the dimensions of the primary and of the secondary retroperitoneal sarcomas (primary sarcoma medium diameter of 167.8 mm and maximum value of 400 mm versus secondary sarcoma medium diameter of 135.38 mm and maximum value of 200 mm). The resecability rate was of 37.5%. Incomplete resections (debulking) (37.5% of all surgical interventions), simple biopsies (21.9%) or laparotomies (3.1%) were done in the remainder of the operated cases. Radical interventions were possible in 15.4% of all operated secondary retroperitoneal sarcomas and in 52.6% of the operated primary retroperitoneal sarcomas (*Table 3*). One of the major causes of primary retroperitoneal tumor unresecability was tumor involvement of the major retroperitoneal vessels. Major blood vessels were involved by the tumor in 42.1% of the primary sarcomas and in 23.1% of the secondary retroperitoneal sarcomas. Instead, secondary retroperitoneal tumors represented advanced tumor stages by extensive invasion or metastasizing of tumors that were

Table 2. *Duration of patient symptoms*

Symptomatic period before patient presentation	**Frequency**	**Percent**
0-3 months	8	61,5%
3-6 months	1	7,7%
6-12 months	2	15,4%
1-2 years	2	15,4%
Total	13	100,0%

Table 3. *Types of surgical interventions in primary and secondary retroperitoneal sarcomas*

Primary sarcoma			Secondary sarcoma		
Intervention	Frequency	Percent	Intervention	Frequency	Percent
Biopsy	4	21,1%	Biopsy	3	23,1%
Debulking	4	21,1%	Debulking	8	61,5%
Laparotomy	1	5,3%	Laparotomy	0	0,0%
Radical	10	52,6%	Radical	2	15,4%
Total	19	100,0%	Total	13	100,0%

Table 4. *Histopathologic types of operated retroperitoneal sarcomas*

Histopathologic type	Frequency	Percent
Adenosarcoma	1	3,1%
Carcinosarcoma	2	6,3%
Chondrosarcoma	2	6,3%
Fibrosarcoma	7	21,9%
Gastrointestinal stromal tumor	2	6,3%
Malignant fibrous histiocytoma	1	3,1%
Leiomyosarcoma	3	9,4%
Liposarcoma	1	3,1%
Undetermined sarcoma	7	21,9%
Rhabdomyosarcoma	1	3,1%
Mixed sarcoma	2	6,3%
Synovial sarcoma	2	6,3%
Endometrial stromal sarcoma	1	3,1%
Total	32	100,0%

initially localized outside the retroperitoneal space and the vascular involvement was not the main cause for unresecability. The average duration of an operation was of 136 minutes, and the median value was of 120 minutes. Apparently tumor involved organs (1 to 6 structures) were resected in 40.6% of all surgical interventions. The most frequently sacrificed organs were: the kidney (in primary sarcomas) and the omentum (in secondary sarcomas). The most frequent histopathologic sarcoma types were: fibrosarcoma (21.9% of all types) and undetermined sarcomas (21.9%). Other histopathologic types are displayed in *Table 4*. However, in the primary sarcomas group the most frequent types were fibrosarcomas, followed by undetermined sarcomas, whereas in the secondary sarcomas, the most common were leiomyosarcomas, gastrointestinal stromal tumors and fibrosarcomas. Both primary and secondary retroperitoneal sarcomas were most frequently poorly differentiated (G3 - 62.5% of all sarcomas). The mean overall survival of operated patients was of 18.74 months, with a median of 7.64 months (mean of 21.86 months for primary sarcomas, 14.17 months for secondary sarcomas). For the radically operated patients the mean overall survival was of 30.9 months versus only 11.44 months for the non-radically operated patients. For the radically operated patients the mean free-recurrence survival was of 20.22 months (median of 7.35 months) and the mean metastasis-free survival was of 26.10 months (median of 13.78 months). Both overall survival and free-disease survival were higher in the radically operated patients with primary retroperitoneal sarcoma than in those with secondary sarcomas. 31.3% of all patients died throughout the study period due to tumor progression with complications. *Table 5* depicts the encountered intraoperative complications (in 16.1% of all operations) during sarcoma surgery. Post-operative complications were recorded in 31.3% of all cases. The average period of stay in the intensive care unit was of 4.6 days. The 5-year overall survival estimate of the entire group of operated patients was of 17%. (*Fig. 1*) There was no significant difference in the survival of the patients with primary or secondary retroperitoneal sarcomas. The 5-year free-recurrence survival

Table 5. *Intraoperative complications*

Intraoperative complications	Frequency	Percent
Rectum lesions	1	16,7%
Haemorrhage from tumor bed	3	30,1%
Spleen lesions	1	16,7%
Inferior vena cava lesion; cecum and right colon devascularization	1	16,7%
Total	6	100,0%

probability for the radically operated patients was of 24%. 50% of the radically operated patients with primary sarcomas had a 48 months free-recurrence survival time, while 50% of the radically operated patients with secondary sarcomas had a free-recurrence survival time of only 13 months. The 5-year free-metastasizing survival estimation was of 18%.

Significant predictors for a higher 5-year overall survival were: the radicality of the intervention, the absence of vascular involvement, tumor dimension less than 150 (mm), operation duration of more than 120 minutes, the absence of tumor antecedents, the association of both radio- and chemotherapy to the surgical treatment, the other variables having no significance in the survival analysis.

For the primary retroperitoneal sarcomas, specific predictors of a higher overall survival were: radicality, absence of vascular involvement (hazard ratio for vascular involvement/ no vascular involvement of 5.9/1), long surgical interventions (more than 120 minutes), female sex (male/female hazard ratio of 4.18) and the adjuvant addition of both radio- and chemotherapy to the surgical treatment. In the radically operated patients, the predictors of a higher 5-year free-recurrence and 5-year free metastasis survival were: female sex and the addition of both adjuvant radio- and chemotherapy to the surgical treatment. For the secondary retroperitoneal sarcomas, the only predictor for a longer overall survival was the addition of complementary treatments.

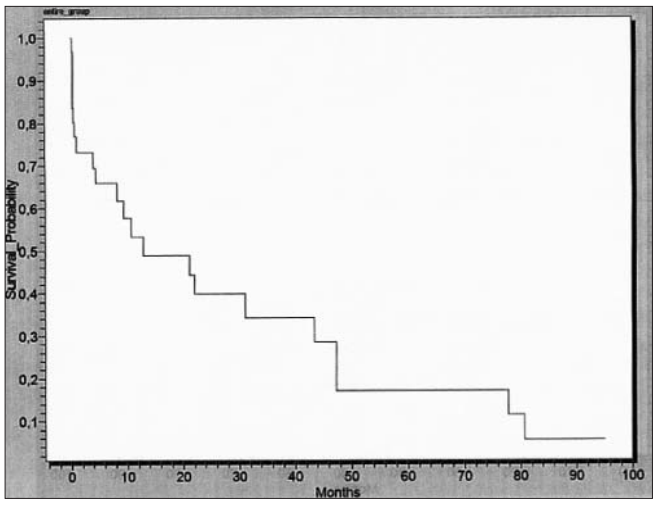

Figure 1. *Overall 5-year survival probability of operated patients with retroperitoneal sarcomas*

Discussions

Retroperitoneal sarcomas are rare and there is insufficient knowledge of these tumors. The only clear aspects in the management of these tumors are that the completeness of surgical resection improves the survival of the patients and that the natural tendency to locoregional recurrences is one of the main causes of death (14). Even in this regard, there is still a certain degree of confusion, since there is no concord on the degree of surgical aggressiveness to be applied to obtain radicality and to prevent recurrences. Also, there is a lack in comparative studies between primary and secondary retroperitoneal sarcoma. The originality of this study results from the fact that we analysed a group of patients with primary and secondary retroperitoneal sarcomas in a unitary, but also in a comparative fashion, to identify characteristics, specific survival predictors, but also common features of presentation and treatment.

In our study, more than half of the cases were represented by primary sarcomas, with a primary/secondary sarcoma ratio of 1.46/1. Both in primary and secondary retroperitoneal sarcoma patients, there was a clear predominance of females, although usually the two sexes are almost equally affected (5). There was no significant difference between the dimensions of primary and secondary retroperitoneal sarcomas. Although both primary and secondary retroperitoneal sarcomas had large dimensions (average diameter of 154.68 (mm)), the resecability rate has not depended on tumor dimension. Although more than half of the sarcomas (62.5%) were G3 tumors, the grading had no impact on resecability or survival rate. The main cause for unresecability in primary tumors was represented by tumor involvement of large retroperitoneal blood vessels ($p = 0.002$) that occurred in 42.1% of primary retroperitoneal sarcomas. Retroperitoneal major blood vessels involvement by the sarcoma has been found by some other authors too as a main cause for unresecability and that predicts a poor prognosis (15, 16). Another cause for primary tumor unresecability was multivisceral involvement. That is why, for an ideal management of such tumors, a multidisciplinary surgical team, specialized in vascular interventions, is necessary (1). Instead, in secondary sarcomas, vascular involvement (in 23.1% of secondary retroperitoneal sarcomas) did not appear as a significant cause for tumor unresecability. The main obstacle of the surgeon in achieving completeness of resection was represented by the already advanced tumor stage of the secondary retroperitoneal sarcoma with multivisceral involvement, making a clear margin resection very difficult. Most secondary retroperitoneal sarcomas were actually initially non-retroperitoneal tumors (digestive or uterine) that directly invaded into the retroperitoneum. A smaller percent of cases were metastases to the retroperitoneum of previously treated extremity or uterine sarcomas (14).

Complete resecability was possible in only 37.5% of all sarcoma cases. The rate of radical resections was significantly higher in primary retroperitoneal sarcomas (52.6% of primary retroperitoneal sarcoma interventions) than in secondary retroperitoneal sarcomas (15.4% of secondary sarcoma interventions) ($p = 0.03$). Resecability rate for primary retroperitoneal sarcomas is within the range of 50 to 95% reported by various centers (2). However, survival rates were not significantly different between the two groups. Completeness of surgical resection has been already proved to be the most important predictor in the survival analysis of patients with retroperitoneal tumors (8,9,17). Achievement of radicality often requires resection of tumor adjacent structures. Although these have been proved to be infiltrated in only 4 to 27% of cases, this approach increases the chances of accomplishing radicality, without negative repercussions on survival rates. In fact, in our study, the occurrence of preoperative complications, the rate of surgical reintervention, the duration of stay in the intensive care unit or the hospitalization period have not proved to be significant predictors in survival analysis for retroperitoneal sarcomas in general, or for primary and secondary sarcomas in particular. Radically operated patients had a significantly higher 5-year overall survival than the other patients (debulking, biopsy, laparotomy). Also, patients with debulking surgery had a significantly lower risk of death than patients that had biopsy or simple laparotomy interventions. (*Fig. 2*) The same observations were made individually for the primary retroperitoneal sarcoma group of patients. This is in contrast with our previous observations on a group of patients with primary retroperitoneal tumors in which we included several histopathologic tumor types and not only sarcomas. In that study, debulking surgery did not bring any benefits in terms of survival in comparison with biopsy or laparotomy interventions (16). The 5-year overall survival estimation for the primary sarcoma group was of 16% and the 50% survival rate was of 10 months. In the secondary retroperitoneal sarcoma group of patients there were no laparotomies, but only radical interventions, debulking and biopsies (15.4%, 61.5%, and 23.1% of all secondary retroperitoneal sarcoma operations). Surprisingly, in this group, there was no significant difference between patients that had radical or non-radical interventions. The 5-year overall survival estimation for this group was of 16% and the 50% survival rate in these patients was of 11.3 months.

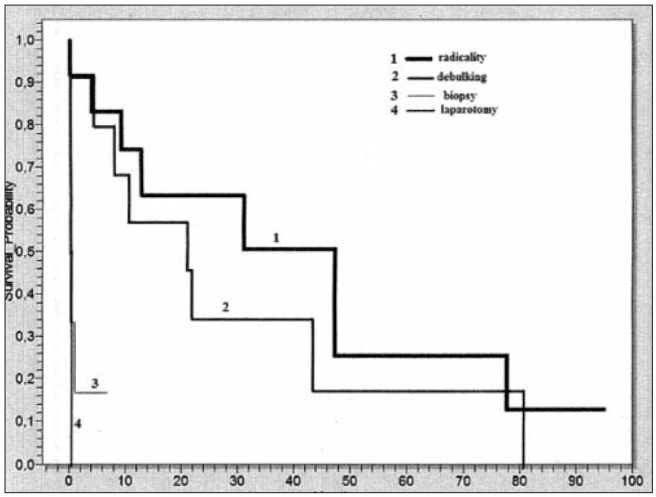

Figure 2. *5-year overall survival rates for patients with radical and non-radical surgical interventions*

Although there was no significant difference in the survival rates of the two groups, in the primary retroperitoneal sarcoma group we found several predictors of an increased survival, some related to the quality and type of the therapeutic scheme. Although resecability was not higher in female patients, still they had a significantly higher survival than male patients. This observation has been made by some other authors, too, while others did not report such a difference (18). Usually, long surgical interventions (more than 120 minutes) represented radical interventions and that is why a long operation was associated with an increased survival of operated patients. We did not find an increase in the survival of patients with well-differentiated liposarcomas. This might be caused by the relative low frequency of this histopathologic type of tumor in our study (3.1% of all sarcomas). Some authors have found grading as a predictor for overall survival. In our study, although G3 was the most frequent tumor grading, it had no significant impact on the overall survival of the patients.

We found that the adjuvant use of both chemo- and radiotherapy to the surgical treatment increased the overall and free-disease survival of operated patients with primary sarcomas. In literature, there are still many controversies and no consensus between centers regarding the utility of complementary treatments (2,9)

In the secondary retroperitoneal sarcomas, the only significant predictors for an increased survival where female sex and the use of adjuvant associated radio- and chemotherapy. Therefore, in such cases, the role of surgery is secondary, and there should be a focus on complementary treatments to increase survival in these patients.

Conclusions

Despite the advances in cancer treatment, resecability, survival rates and surgery results remain unsatisfactory for the patients with retroperitoneal sarcomas. We found that in primary retroperitoneal sarcoma we can intervene more to increase patient survival by targeting radicality and adding complementary treatments. Radicality can be achieved by choosing to perform multivisceral and vascular resections, followed by various reconstructions, and by multidisciplinary experienced therapeutic teams. Retroperitoneal major blood vessel involvement by the tumor remains a main cause of unresecability in primary retroperitoneal sarcomas, and therefore future focus of surgical centers should be in increasing the level of experience and courage in performing vascular interventions. Instead, in secondary retroperitoneal sarcomas, vascular involvement plays a smaller role and usually the impressive extension of the tumors makes very difficult to obtain negative surgical margins. 5-year overall survival is not different for the two groups. The only common, apparently unexplainable prognostic factor for a higher overall survival for the two groups is female gender.

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