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Long-Term Outcomes in Treatment of Retroperitoneal Sarcomas: A 15 Year Single-Institution Evaluation of Prognostic Features

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Abstract

Background—Retroperitoneal sarcomas are connective tissue tumors arising in the retroperitoneum. Surgical resection is the mainstay of treatment. Debate has arisen over extent of resection, changes in histological classification/grading, and interest in incorporating radiotherapy. Therefore, we reviewed our institution's experience to evaluate prognostic factors.

Methods—Retrospective chart review of all primary RPS patients at Johns Hopkins Hospital from 1994 – 2010. Histologic diagnosis and grading were re-evaluated with current criteria. Prognostic factors for survival, and recurrence were assessed.

Results—131 primary RPS patients met inclusion criteria. Median survival for patients who undergo en-bloc resection to negative margins (R0/R1) is 81.7 months. Surgical margins and grade were the most important factors for survival along with age, gender, presence of metastases and resection of 5 organs. 5 year survival for R0/R1 resection was 60%, similar to compartmental resection. Radiotherapy significantly decreased local recurrence ($p=0.026$) on multivariate analysis. Grade in leiomyosarcomas and dedifferentiation in liposarcomas dictated patterns of local vs distal recurrence.

Conclusions—En bloc surgical resection to R0/R1 margins remains the cornerstone of therapy and provides comparable outcomes to compartmental resections. Grade remains important for prognosis, and histology dictates recurrence patterns. Radiotherapy appears promising for local control and warrants further investigation.

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Keywords

Liposarcoma; Leiomyosarcoma; Sarcoma; Compartmental Resection; Radiation; Grade

Background

Retroperitoneal sarcomas (RPS) are a rare entity, comprising 10–16% of soft tissue sarcomas (STS) [1–3]. The main tenet of treatment for all STS is complete surgical resection to negative margins. This gives the best chance for cure and long term survival. However, due to the anatomy of the retroperitoneal space, RPS presents a unique challenge. Tumors often remain undetected for extended periods of time and frequently invade or encase surrounding organs making complete resection difficult [4–6]. RPS has a greater rate of local recurrence than extremity sarcomas [7] and survival rate 20–40% of an equivalent extremity STS [8].

Radiation therapy (RT) and compartmental resection are two mechanisms for local control that have been promulgated in the RPS literature over the past decade [9]. The difficulty of RT in RPS arises from its toxicity on radiation-sensitive organs such as the kidneys, small bowel, liver and spine [4]. The most promising approaches are preoperative External Beam Radiation Therapy (EBRT) along with Intraoperative Radiation Therapy (IORT), which can give higher doses of radiation directly to the area of resection with minimal involvement of surrounding organs [10]. Multiple studies have shown significant improvement in local recurrence rates with IORT and preoperative EBRT, however this did not translate into significant differences in overall survival compared to surgery alone [11–14].

Because of the invasion or envelopment of adjacent organs in RPS, surgery frequently includes resection of involved organs to achieve negative margins [9]. The goal of surgery in all sarcomas is to achieve R0, or microscopically negative margins, ideally with a rim of normal tissue. However, R0 resections are often difficult or impossible to attain with large lesions, and R1 resections may provide comparable results. Compartmental resection has been advocated by several centers as a method to improve prognosis. This is a surgical technique in which the retroperitoneum is treated similar to an extremity compartment and the tumor is completely excised en bloc along with the ipsilateral colon, kidney, and/or psoas muscle, regardless of involvement, to achieve widely negative margins [15]. Two major retrospective European studies evaluating the efficacy of compartmental resection showed a decrease in local recurrence rates compared to traditional complete resection, but without a significant improvement in overall survival [15,16]. Critics have pointed out that organs commonly removed in compartmental resection are easily resectable while other equally adjacent structures such as the pancreas, duodenum, aorta, and IVC, were not routinely resected en bloc. Routine resection of these would be more difficult and could increase morbidity and mortality [17]. Additionally, it has been hypothesized that in some patients with liposarcomas which recur in locations remote from the primary tumor, but not distant metastases, there exists a field defect for which frontline compartmental resection would be unnecessary and not beneficial [18]. Therefore, critics point out that compartmental

resection extends some, but not all, resection margins around the tumor with questionable benefit.

In addition to changing treatments, there have been recent changes in the pathologic diagnosis and grading of RPS. Certain histologic subtypes confer a worse prognosis for survival and recurrence when compared to well-differentiated liposarcomas (WDLPS). One of the most common of these was malignant fibrous histiocytoma (MFH), a classification that has been rendered obsolete over the past decade. The majority of MFH in the retroperitoneum are now recognized and reclassified as undifferentiated pleomorphic sarcomas (UPS) or dedifferentiated liposarcomas (DDLPS), and correctly reclassifying an MFH/UPS into a DDLPS may require molecular testing [19–23]. Additionally, the 7th edition of the American Joint Committee on Cancer changed the grading criteria for sarcomas from a four to a three-grade system, classifying sarcomas as low, intermediate, and high grade [24]. These changes in diagnosis must be evaluated for their association with outcomes.

Given the rarity of retroperitoneal sarcomas, most studies on this disease either have small sample size or are multi-institutional and derived from administrative data. Therefore, they are confounded by inconsistencies in care and inaccurate information. This study was designed as a large single-center study to comprehensively evaluate prognostic factors for retroperitoneal sarcoma in the context of recent changes in surgical approach, pathologic grading, histologic diagnosis and use of radiotherapy.

Methods

Study Population

The pathology records and the cancer registry were queried for the diagnosis “retroperitoneal sarcoma.” The charts of all patients were reviewed. All research was performed with the approval of the institutional review board. Inclusion criteria was any patient above 18 years of age diagnosed with a primary, unifocal, retroperitoneal sarcoma without sarcomatosis at the Johns Hopkins Hospital between January 1994 and December 2010 who underwent management at Johns Hopkins Hospital. All gastrointestinal stromal tumors (GIST), desmoid tumors, and lymphomas were excluded. Follow up for all patients continued until February 2015. Surgical patients underwent attempted tumor resection which included macroscopically involved adjacent organs when necessary. No compartmental resection was performed. However, all the regional fat surrounding the index tumor was removed at the time of the resection. Surgical margins were classified as R0 if margins were microscopically negative, R1 if there was microscopic tumor on inked margins or within <1mm from the inked margin, and R2 if there was gross residual tumor left behind.

Pathologic Evaluation

A single pathologist (EAM) with expertise in the field of sarcomas examined all available pathologic specimens at the time of the study using WHO criteria and AJCC 7th edition to determine histology and tumor grade [24,25]. Tumors previously diagnosed as MFH were reclassified after pathologist re-evaluation of slides, nearly all to dedifferentiated

liposarcomas, although no molecular testing was performed on these samples. None of the tumors were reclassified as undifferentiated pleomorphic sarcoma. Tumors classified as Sarcoma NOS were unable to be grouped into a specific subtype and/or slides were not available for pathologist re-evaluation, and nearly all of these (7/10) were high grade sarcomas.

Statistical Analysis

Overall survival was measured as time from date of diagnosis to date of death or last follow up. Patients lost to follow-up were censored at that day. Patient records and social security death index were used. Recurrence was only analyzed in patients who had R0 or R1 resection. Local recurrence was defined as recurrence at or near the location of the primary tumor. Distal recurrence was defined as recurrence in a location distal from the original site, most commonly liver, lung, or bone. Patients lost to follow up immediately after surgery were not included in analysis for recurrence. Patients who had unclear surgical margins but at least R0/R1 were listed as “Unknown” as a placeholder for multivariate analysis and included in the recurrence analysis. Patients with missing data for resection margins or tumor grade had placeholder values labelled “Unknown” which was included in the statistical analysis. Survival was illustrated using the Kaplan-Meier method, log-rank tests and the association of covariates. Survival was calculated from time of diagnosis to event (recurrence or all-cause mortality) or last follow-up. Univariate Cox regression models were used to estimate relative hazards between specific covariates and recurrence or all-cause mortality. Tests for interactions were performed on clinically relevant covariates. Two statistical models were run for multivariate analysis of survival: one analyzing all RPS patients cumulatively and another analyzing only surgical patients to assess surgically significant factors. Results of Cox regression were reported as hazard ratios (HR) with 95% confidence intervals (CIs). Statistical analyses and graphic renderings were performed using the STATA 10.0 statistical software [26].

Results

Patient Population

There were 228 patients with a diagnosis of primary RPS at Johns Hopkins Hospital from 1994 to 2010. 131 of these patients met all inclusion criteria for the study. Females comprised 51.1%. Median age at diagnosis was 59 years. 26 patients (19.5%) presented with metastases (Table 1).

Histology

The most common histologies were leiomyosarcoma (LMS, 39.7%), and liposarcoma (LPS, 38.2%), comprising over 75% of the tumors. Of the liposarcomas, 2/3 were dedifferentiated liposarcomas (DDLPS, 24.4%) and 1/3 well-differentiated (WDLPS, 13.5%) (Table 1). The next most common histology was Sarcoma, NOS comprising 7.6% of the series. Seventy percent of the Sarcoma NOS were high grade tumors. Median tumor size was 12.3 cm and the largest tumor was 47.3 cm. The majority of patients had information on grade available (n = 119, 90.8%) and grade 3 was most common (52.7%) followed by grade 2 (20.6%) and then grade 1 (17.6%). Grade information was unknown in 12 cases (9.6%). (Table 1).

Twenty three patients (17.6%) had metastatic disease on initial presentation and the most common histology for these patients was LMS (43.5% of metastatic patients) followed by DDLPS and Sarcoma NOS (17.4% each). Sites of metastases included liver only (7/23), lung only (3/23), liver and lung (6/23), and other sites (i.e. bone, adrenal, pleural, 7/23).

Treatment

Nearly all patients (87.8%) underwent attempted complete surgical resection after initial presentation (n =115, Table 1). Margins of resection were either R0 or R1 in 84.4% of all surgical patients. R2 resection was present in 15.6%. Patients with metastases also had a high surgery rate (60.9% of metastatic patients; n=14). Of the metastatic surgical patients, half of these patients (n=7) also underwent resection of their metastatic loci along with resection of the primary, and all 7 of these patients had R0/R1 margins.

The majority of surgical patients had at least 1 organ resected (81.4%, Table 1). Median number of organs removed was 2 and maximum was 6. The most frequently resected organ was the kidney (44.4% of surgical patients) followed by colon (21.7%). Inferior vena cava resections were performed in 15.7% of surgical patients and 8 patients (6.8%) underwent a pancreaticoduodenectomy (or Whipple procedure) as part of their resection. (Table 1)

A fraction of all patients received chemotherapy or radiation therapy (n =31 or 23.7% and n=37 or 28.2% respectively, Table 1). Of those receiving radiation, 29% received preoperative radiotherapy, 48% received postoperative, 13% received a combination of preoperative and intraoperative radiotherapy, and 10% received radiotherapy without surgery. External Beam Radiation Therapy (EBRT) with photons was most commonly used, and doses administered were between 40 – 50.4 Gy, while intraoperative radiotherapy doses were 10 – 12 Gy. Radiotherapy was often given preoperatively for tumors where there was concern that negative margins would be difficult to obtain along with intraoperative radiation. Postoperative radiation was delivered for close margins. Radiotherapy was given to 25% of DDLPS patients, 23% of LMS, 11% of WDLPS, and 40% of Sarcoma NOS. 37 out of 131 patients received chemotherapy. 34.4% of DDLPS, 28.9% of LMS, and 50% of Sarcoma NOS received chemotherapy. Chemotherapy was not given to any patients with WDLPS. The most commonly used chemotherapy regimens were either MAI (Mesna, Adriamycin, Ifosfamide) or gemcitabine and docetaxel.

Overall Survival

Median overall survival was 48.7 months for all patients (95% CI 33.7 – 66.3). Median survival in patients who underwent surgery was 62.7 months compared to 12.7 months in those who did not (p<0.001, Figure 1A). Median survival for resection to negative margins (R0/R1) was 73.5 months compared to 10.1 months in R2 resections (p<0.001). The difference in survival between R0 and R1 groups was not significant (p=0.862). Importantly, the median overall survival for the R2 group was not significantly different from the group who did not undergo surgery (p=0.421, Figure 1A). Finally, median survival for R0/R1 resection in patients who presented without metastases was 81.7 months (95% CI 57.9 – 126.4).

Cox proportional hazards analysis was performed for overall survival in the entire cohort of patients (n=131) and then in patients who underwent surgical resection only (n= 115) (Table 2). In analyzing the factors associated with survival for the entire cohort (n=131), male gender (HR 2.00, p=0.012 Table 2), age above 60 (HR 2.00, p=0.009 Table 2), presence of metastases (HR 4.50, p<0.001 Table 2), R2 resection (HR 6.51, p<0.001 Table 2) or no resection (HR 8.24, p<0.001 Table 2), and high grade (HR 2.20, p=0.007 Table 2) were significantly associated with worse OS. Radiotherapy administration was significantly associated with improved OS (HR 0.53, p = 0.046 Table 2).

Focusing only on the subset of patients who underwent surgical resection (n=115), male gender was again associated with greater risk of death (HR 2.76, p=0.002 Table 2), as well as age>60 (HR 2.61, p=0.002 Table 2) and presence of metastases (HR 4.79, p=0.001 Table 2). Patients who had R2 resection margins had significantly increased risk of death and similar survival to those who did not undergo surgery on Kaplan Meier (HR 6.66, p<0.001, Table 2; Figure 1A). However, R1 margins were not significantly associated with survival. Resection of 5 or more organs increased risk of death compared to no organs resected (HR 6.25, p=0.005), but not any number of organs less than that.

High grade lesions had significantly increased risk of death (HR 2.01 p=0.022, Table 2). In surgical patients, high grade lesions had a 5 year survival of 35%, compared to 70% for intermediate and 75% for low grade lesions (p=0.021, Figure 1B). Additionally, if one considers only those patients resected to R0/R1 margins, the 5 year survival in low grade lesions increases to 82%, and intermediate to 77%, compared to 43% 5 year survival in patients with higher grade tumors. The difference between low/intermediate and high grade lesions was again statistically significant (p=0.040). Overall, in surgical patients resected to R0/R1, median survival for high grade lesions was 50.5 months compared to 89.2 months in low/intermediate grade lesions.

Histology of DDLPS and LMS had hazard ratios indicating increased risk of death compared to WDLPS, however these results were not significant on multivariate analysis (Table 2). This is due in large part to the interaction of grade with histology and greater effect of high grade on survival. To illustrate this point, in all patients where grade was available, there were no WDLPS classified as high grade, while 61.3% of DDLPS and 70.0% of LMS were classified as high grade tumors (p<0.001). Additionally, due to the small numbers individually, we combined all other histologic subtypes that were not liposarcomas or leiomyosarcomas into a group labeled “Other” for analysis. Of note, of the patients in the “Other” group whose grade was known, 68.2% were high grade lesions.

Finally, radiotherapy was a significant factor for survival in the all patients group but not the surgical patient’s only group. The hazard ratios for radiotherapy in the 2 groups was nearly identical, however, which reflects that the surgical group may have been underpowered due to low numbers (HR 0.53 p=0.046, HR 0.57 p=0.122, Table 2).

In a subgroup analysis, median survival for metastatic patients who underwent metastatectomy, all of whom achieved R0/R1 resection, was not significantly different from surgical patients without metastases (54.6 months vs 68.2 months respectively, p = 0.067).

When comparing this group to non-metastatic patients resected to R0/R1, there is a significant difference in median survival (54.6 months vs 81.7 months, $p = 0.018$), however this is still a marked improvement over the dismal outcome of metastatic patients who could not get R0/R1 resection (median survival 2.97 months, 95% CI 0.71 – 8.97). This suggests a role for surgery and metastatectomy in select patients presenting with primary metastatic RPS.

Overall Recurrence

Recurrence was evaluated in the non-metastatic patients who had undergone successful surgical resection to R0/R1 margins ($n=97$). Ten patients who were resected to R0/R1 margins were lost to follow up shortly after surgery and were excluded from the analysis, leaving 87 patients for recurrence analysis. Median overall RFI for any recurrence, either local or distant, was 20.0 months. Median RFI for any recurrence in R0 resection was 35.9 months, compared to 18.2 months for R1 resection ($p = 0.042$ by log-rank test). Median RFI for any recurrence in WDLPS was 70.1 months compared to 29.6 months for DDLPS and 17.1 months for LMS ($p=0.051$). Median RFI for patients with metastases was only 9.74 months compared to 24.4 months for patients without metastases ($p<0.001$). Median RFI when no organs were resected was 70.1 months compared to 17.5, 16.1, and 14.7 months when 1–2, 3–4, and 5 organs were resected, respectively, although this was not significant ($p=0.083$).

On multivariate analysis, margin status (R1 margin HR 4.28, $p<0.001$ Table 3), size of tumor $>15\text{cm}$ (HR 4.38, $p=0.024$ Table 3) and presence of metastases (HR 6.61, $p=0.003$ Table 3) were associated with increased risk of recurrence. Histology of LMS (HR 4.09, $p=0.019$ Table 3) or Other (HR 5.17, $p=0.015$ Table 3) also increased recurrence. Number of organs resected did not increase recurrence risk until 5 or more organs were resected (HR 17.8, $p<0.001$ Table 3). No individual organ alone showed a significantly increased risk of recurrence.

Local vs. Distant Recurrence

Given that the factors influencing local vs distal recurrence are disparate, we next analyzed recurrence patterns for local and distal recurrence separately, evaluating variables relevant to each. Organs were individually assessed for risk of recurrence through univariate analysis, and each organ that was significantly associated with increased risk of local or distal occurrence on univariate analysis was included in the multivariate model. Significant factors for local recurrence on multivariate analysis were administration of radiotherapy (HR 0.28 $p=0.026$, Table 4, Figure 2B), R1 margin (HR 3.82 $p=0.007$, Table 4), and diaphragmatic resection (HR 18.4 $p=0.002$, Table 4). Histology of DDLPS approached significance on local recurrence analysis (HR 2.50 $p=0.061$, Table 4) but LMS did not. Local RFI for WDLPS was 70.1 months compared to 29.6 months for DDLPS (Figure 2A). Although this difference was not significant histology as a factor overall was significant for local recurrence ($p=0.0001$, Figure 2A). For distal recurrence, median RFI in high grade tumors was 19.4 months, compared to 89.8 months in intermediate grade and median was not reached in low grade (Figure 3B). In LMS, median distant RFI was 20 months. 21.7% of DDLPS ever had a distant recurrence, and no WDLPS patient had a distant recurrence

($p<0.0001$, Figure 3A). Factors which significantly increased recurrence risk on multivariate analysis were male sex (HR 2.31 $p=0.035$, Table 5), presence of metastases (HR 8.09 $p=0.004$, Table 5), any histology other than WDLPS ($p<0.001$, Table 5), size greater than 15cm (HR 4.93 $p=0.032$, Table 5), and high grade (HR 2.52 $p=0.033$, Table 5). Diaphragm resection was again significantly associated with increased risk of distant recurrence on both univariate and multivariate analysis, (HR 15.1, $p=0.013$).

Discussion

RPS remains a rare disease and while previous studies have advanced our knowledge, [27–29] most are either out of date, multi-institutional, or derived from administrative data. This current study examined 131 primary RPS patients treated at Johns Hopkins Hospital and constitutes one of the largest single-institution studies over the past 15 years. We sought to provide updated information on RPS survival and recurrence in a consistent setting. This is particularly important in the face of the current re-evaluation of optimal disease management and changing definitions in grading and pathology [20]. Our study demonstrated the importance of surgical margins and histology in survival and recurrence patterns, and a recent study also confirmed similar results [30]. However, we evaluated grade and histology separately in our study, highlighting the increased significance of dedifferentiation and histology in local recurrence and grade in distal recurrence patterns. Additionally, we examined surgical and nonsurgical groups separately for factors contributing to overall survival.

Historically, the 5-year survival rate and local control rate have varied widely depending on the series, ranging between 40–80% and 50–70%, respectively [2]. R0 margins are an acknowledged positive prognostic factor, associated with improved overall survival and local control [31–33]. Recently, surgeons in some high volume centers have routinely performed compartmental resection. Their overall 5-year survival is 60–65% [15,16,34] and local recurrence was improved with recurrence rate at 3 years of 10% [34] and at 5 years of 20–30% [15,16]. In a study by Gronchi *et al*, recent patients who had undergone compartmental resection were compared to past patients who had not, and while no survival benefit was seen in high grade lesions, improvement in 5 year survival was demonstrated in low grade (72.6% to 90.7%) and intermediate grade (37.7% to 74.1%) lesions [35]. These survival rates by grade are comparable to our rates in this study. However, there is uncertainty concerning the necessity of such a procedure, particularly since overall survival was not improved [17,36].

Our institution does not routinely perform compartmental resections. Instead, surgeons have focused on performing oncologic resection to negative margins, including involved organs when necessary. Patients with metastatic disease that is amenable to resection undergo metastatectomy. The results of this study indicate that resection to R0/R1 margins provided a 5-year overall survival of 60%, comparable to that of compartmental resection and in line with other previously reported series. Additionally, our 5 year survival rate for R0/R1 resection in low grade lesions (82%), intermediate (77%) and high grade (43%) is comparable to the improved rates reported with compartmental resection [35]. R2 resections were found to be significantly associated with poor overall survival of similar duration to

those not undergoing surgery. R1 resection did not significantly increase risk of death but significantly increased risk of local recurrence. Therefore, this suggests that surgical resection should be performed to achieve ideally R0 but at minimum R1 margins. However, there is no role for debulking to R2 margins except in palliative surgery. Metastases do not preclude patients from surgery if they are able to be resected to R0/R1 margins with metastatectomy, as this provided a significant survival benefit. While these patients did have lower survival than patients without metastases, the 5-year survival rate was still 40%, with median survival of 54.6 months, and was superior to the dismal median survival of 2.97 months for metastatic patients who were not able to undergo surgery and metastatectomy. Furthermore, with our approach, the number of organs resected did not affect survival or recurrence until it was greater than five. Not surprisingly, R1 margins significantly increased the risk of local recurrence, but not distal recurrence. However, the true benefit of incorporating compartmental resection may lie here, in this increased risk of local recurrence and thus re-resection with R1 margins. Compartmental resection may be capable of achieving achieve R0 margins more consistently to decrease local recurrence rates, which has been demonstrated in prior studies, but whether this ultimately effects survival is still unclear. Finally, no individual organ, including IVC and Whipple, affected recurrence, either local or distal, except for diaphragm resection, which affected both. However, there were only 5 diaphragm resections in this patient cohort, so it is difficult to draw any definitive conclusions based on this result.

The majority of radiotherapy performed at this institution was given in the most recent decade most frequently for DDLPS, LMS, and Sarcoma NOS. This highlights a recent interest in integrating radiotherapy, especially IORT and preoperative EBRT or IMRT, to achieve better local control. There are still many questions regarding the optimal method of administration, as well as which subset of patients would benefit. In our cohort of 31 patients that received RT, there was a significant improvement in risk of local recurrence (HR 0.28, $p=0.026$). This is consistent with other published literature regarding improved local control rates with radiotherapy. Additionally, there was also a borderline significant improvement in survival with radiotherapy (HR 0.53, $p=0.046$), but this result should be interpreted with caution, as this was a small sample size in a retrospective review. Nevertheless, the result is intriguing and warrants further investigation with larger cohorts and well-designed prospective randomized trials, especially in administering preoperative RT with IORT in liposarcomas to achieve improved local control and survival. A phase III randomized controlled trial by the European Organization for Research and Treatment of Cancer (EORTC) is currently ongoing in which retroperitoneal sarcoma patients are randomized to receive either surgery alone or preoperative radiotherapy with 3D Conformation Radiotherapy (3D-CRT) or IMRT to a dose of 50.4 Gy followed by surgical resection. (clinicaltrials.gov) Additionally, given that other institutions have also demonstrated improved local control rates with radiotherapy and compartmental resection independently, it would be beneficial to study compartmental resection in combination with preoperative radiotherapy and IORT as a strategy of potentially providing the most ideal local control rates and potentially improving survival. However, a combination of aggressive and potentially unnecessary organ resection with aggressive radiation may lend itself to increased toxicity and complications. A limitation of our study is that we had incomplete

data regarding toxicity of radiotherapy due to the fact that patients often received preoperative or postoperative EBRT at outside institutions with surgery and surgical follow up at our institution, so information on toxicity or complications from radiotherapy was often unavailable.

The influence of tumor histology and grade have previously been discussed in the literature, but changes in nomenclature and grading criteria have made longitudinal evaluations difficult. High grade was again seen as a highly significant factor for overall survival. However, there is a high degree of interaction between histology and grade, with WDLPS being uniformly low grade, while DDLPS and LMS have a high percentage of high grade lesions. Therefore, when evaluating recurrence patterns, histology and degree of dedifferentiation were important for local recurrence, as liposarcomas and DDLPS are much more likely than LMS to recur locally. LMS was the most likely to recur distally, along with DDLPS to a lesser degree, and grade was a highly significant factor in distal recurrence. DDLPS also increased risk of distal recurrence, but to a lesser degree than LMS. Notably, grade is particularly important in predicting distal recurrence, indicating that high grade LMS is much more likely to have distant metastases than low or intermediate grade. Additionally, the “Other” group of histology showed significantly worse survival and recurrence. This group contained a large proportion of Sarcoma NOS, a group of tumors that was unable to be characterized, poorly differentiated, and nearly all high grade, indicating that grade played a role in the outcomes of this group as well.

Limitations of this study include its nature as a retrospective chart review. Some patients had incomplete or missing data, especially regarding resection margins or grade, and had placeholders when performing multivariate analysis. Information on follow up was also incomplete for some patients who either did not follow up or underwent postoperative care at outside institutions. The number of patients receiving radiation in this study was too small to draw any definitive conclusions, but merely generates a hypothesis, and information on toxicity of radiotherapy was unavailable. Additionally, the histologic subtypes other than liposarcoma and leiomyosarcoma had numbers too low to draw definitive conclusions individually and grouping them together was necessary for analysis but may mask the outcome of a single especially detrimental or beneficial histology.

Conclusion

Our institution’s strategy of tumor resection including involved organs and metastases had overall survival comparable to compartmental resection. Our study reiterated the importance of surgical management in RPS and resection to at least R1, but ideally R0 margins. R1 margins also increased risk of local recurrence. If grossly negative margins are not possible, then only palliative surgery should be performed if necessary. The next most important variable for survival was grade, with high grade significantly increasing risk of death. Histology was important for recurrence and patterns of recurrence, with WDLPS showing the best outcomes in survival and recurrence, DDLPS causing increased local recurrence risk, and LMS increasing distant recurrence. Grade was also an important predictor of distant recurrence. Radiotherapy significantly decreased local recurrence on multivariate analysis, with a borderline significant decreased risk of death on multivariate analysis,

however these results should be interpreted with caution as this result was from small sample size. Follow up prospective trials including preoperative EBRT and IORT are warranted. We believe our results are generalizable and applicable to other tertiary care institutions with similar capabilities and RPS volumes.

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References

1. Dalton RR, Donohue JH, Mucha P Jr, et al. Management of retroperitoneal sarcomas. *Surgery*. 1989; 106:725–732. discussion 732–723. [PubMed: 2799648]
2. Kneisl JS, Coleman MM, Raut CP. Outcomes in the management of adult soft tissue sarcomas. *Journal of surgical oncology*. 2014
3. Brennan MF, Antonescu CR, Moraco N, Singer S. Lessons learned from the study of 10,000 patients with soft tissue sarcoma. *Annals of Surgery*. 2014; 260:416–422. [PubMed: 25115417]
4. Bartlett E, Yoon SS. Current treatment for the local control of retroperitoneal sarcomas. *Journal of the American College of Surgeons*. 2011; 213:436–446. [PubMed: 21723153]
5. Singer S, Corson JM, Demetri GD, et al. Prognostic factors predictive of survival for truncal and retroperitoneal soft-tissue sarcoma. *Ann Surg*. 1995; 221:185–195. [PubMed: 7857146]
6. Grobmyer SR, Wilson JP, Apel B, et al. Recurrent retroperitoneal sarcoma: impact of biology and therapy on outcomes. *Journal of the American College of Surgeons*. 2010; 210:602–608. 608–610. [PubMed: 20421013]
7. van Doorn RC, Gallee MP, Hart AA, et al. Resectable retroperitoneal soft tissue sarcomas. The effect of extent of resection and postoperative radiation therapy on local tumor control. *Cancer*. 1994; 73:637–642. [PubMed: 8299085]
8. Singer S, Demetri GD, Baldini EH, Fletcher CD. Management of soft-tissue sarcomas: an overview and update. *The Lancet Oncology*. 2000; 1:75–85.
9. Olimpiadi Y, Song S, Hu JS, et al. Contemporary Management of Retroperitoneal Soft Tissue Sarcomas. *Curr Oncol Rep*. 2015; 17:39. [PubMed: 26092408]
10. Koshy M, Landry JC, Lawson JD, et al. Intensity modulated radiation therapy for retroperitoneal sarcoma: a case for dose escalation and organ at risk toxicity reduction. *Sarcoma*. 2003; 7:137–148. [PubMed: 18521378]
11. Sindelar WF, Kinsella TJ, Chen PW, et al. Intraoperative radiotherapy in retroperitoneal sarcomas. Final results of a prospective, randomized, clinical trial *Archives of surgery (Chicago, Ill: 1960)*. 1993; 128:402–410.
12. Stucky CC, Wasif N, Ashman JB, et al. Excellent local control with preoperative radiation therapy, surgical resection, and intra-operative electron radiation therapy for retroperitoneal sarcoma. *Journal of surgical oncology*. 2014; 109:798–803. [PubMed: 24862926]
13. Pawlik TM, Pisters PW, Mikula L, et al. Long-term results of two prospective trials of preoperative external beam radiotherapy for localized intermediate- or high-grade retroperitoneal soft tissue sarcoma. *Annals of surgical oncology*. 2006; 13:508–517. [PubMed: 16491338]
14. Krempien R, Roeder F, Oertel S, et al. Intraoperative electron-beam therapy for primary and recurrent retroperitoneal soft-tissue sarcoma. *International journal of radiation oncology, biology, physics*. 2006; 65:773–779.
15. Bonvalot S, Rivoire M, Castaing M, et al. Primary retroperitoneal sarcomas: a multivariate analysis of surgical factors associated with local control. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2009; 27:31–37. [PubMed: 19047280]

16. Gronchi A, Lo Vullo S, Fiore M, et al. Aggressive surgical policies in a retrospectively reviewed single-institution case series of retroperitoneal soft tissue sarcoma patients. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2009; 27:24–30. [PubMed: 19047283]
17. Pisters PW. Resection of some -- but not all -- clinically uninvolved adjacent viscera as part of surgery for retroperitoneal soft tissue sarcomas. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2009; 27:6–8. [PubMed: 19047279]
18. Tseng WW, Madewell JE, Wei W, et al. Locoregional disease patterns in well-differentiated and dedifferentiated retroperitoneal liposarcoma: implications for the extent of resection? *Ann Surg Oncol*. 2014; 21:2136–2143. [PubMed: 24705628]
19. Fabre-Guillevin E, Coindre JM, de Somerhausen NS, et al. Retroperitoneal liposarcomas: follow-up analysis of dedifferentiation after clinicopathologic reexamination of 86 liposarcomas and malignant fibrous histiocytomas. *Cancer*. 2006; 106:2725–2733. [PubMed: 16688768]
20. Park JO, Qin LX, Prete FP, et al. Predicting outcome by growth rate of locally recurrent retroperitoneal liposarcoma: the one centimeter per month rule. *Ann Surg*. 2009; 250:977–982. [PubMed: 19953716]
21. Fletcher CD, Gustafson P, Rydholm A, et al. Clinicopathologic re-evaluation of 100 malignant fibrous histiocytomas: prognostic relevance of subclassification. *J Clin Oncol*. 2001; 19:3045–3050. [PubMed: 11408500]
22. Delisca GO, Mesko NW, Alamanda VK, et al. MFH and high-grade undifferentiated pleomorphic sarcoma-what's in a name? *Journal of surgical oncology*. 2014
23. Chouairy CJ, Abdul-Karim FW, MacLennan GT. Retroperitoneal liposarcoma. *J Urol*. 2007; 177:1145. [PubMed: 17296434]
24. AJCC Cancer Staging Manual. 7. Springer-Verlag; New York: 2010.
25. Fletcher, CDMUK.; Mertens, F. *Cancer IAFRo. Pathology and Genetics of Tumours of Soft Tissue and Bone*. Lyon, France: LIPS; 2006.
26. Stata Statistical Software. College Station, Tx: StatCorp LP; 2007.
27. Cody HS 3rd, Turnbull AD, Fortner JG, Hajdu SI. The continuing challenge of retroperitoneal sarcomas. *Cancer*. 1981; 47:2147–2152. [PubMed: 7226108]
28. Lewis JJ, Leung D, Woodruff JM, Brennan MF. Retroperitoneal soft-tissue sarcoma: analysis of 500 patients treated and followed at a single institution. *Ann Surg*. 1998; 228:355–365. [PubMed: 9742918]
29. Kilkenny JW 3rd, Bland KI, Copeland EM 3rd. Retroperitoneal sarcoma: the University of Florida experience. *Journal of the American College of Surgeons*. 1996; 182:329–339. [PubMed: 8605556]
30. Tan MC, Brennan MF, Kuk D, et al. Histology-Based Classification Predicts Pattern of Recurrence and Improves Risk Stratification in Primary Retroperitoneal Sarcoma. *Ann Surg*. 2015
31. Cho SY, Moon KC, Cheong MS, et al. Significance of microscopic margin status in completely resected retroperitoneal sarcoma. *J Urol*. 2011; 186:59–65. [PubMed: 21571334]
32. Strauss DC, Hayes AJ, Thway K, et al. Surgical management of primary retroperitoneal sarcoma. *Br J Surg*. 2010; 97:698–706. [PubMed: 20306527]
33. Paryani NN, Zlotecki RA, Swanson EL, et al. Multimodality local therapy for retroperitoneal sarcoma. *Int J Radiat Oncol Biol Phys*. 2012; 82:1128–1134. [PubMed: 21664065]
34. Bonvalot S, Miceli R, Berselli M, et al. Aggressive surgery in retroperitoneal soft tissue sarcoma carried out at high-volume centers is safe and is associated with improved local control. *Annals of surgical oncology*. 2010; 17:1507–1514. [PubMed: 20393803]
35. Gronchi A, Miceli R, Colombo C, et al. Frontline extended surgery is associated with improved survival in retroperitoneal low- to intermediate-grade soft tissue sarcomas. *Ann Oncol*. 2012; 23:1067–1073. [PubMed: 21765179]
36. Raut CP, Swallow CJ. Are radical compartmental resections for retroperitoneal sarcomas justified? *Ann Surg Oncol*. 2010; 17:1481–1484. [PubMed: 20401636]

Synopsis

Retroperitoneal sarcoma (RPS) management has undergone significant changes with regard to histological diagnosis and grading, and there is ongoing controversy regarding the extent of resection. We reviewed all primary RPS patients over the last 15 years at Johns Hopkins Hospital and determined relevant factors for survival and recurrence. En-bloc resection was not inferior to compartmental resection in this series. The most important prognostic factors are margin status and grade and histology dictates recurrence patterns. Radiotherapy was used selectively but showed improvement in local recurrence.

Figure 1.
A. Survival by different surgical margin status B. Survival by different grades in surgical patients with known grade

Figure 2.
A. Local Recurrence Free Interval (RFI) by histology B. Local RFI by administration of radiotherapy

Figure 3.
A. Distant Recurrence Free Interval (RFI) by histology B. Distant RFI by different grades

Table 1

Retroperitoneal Sarcoma Patient Characteristics

Variable (n)	Number	%	Percent
Sex			
Male	63		48.1
Female	68		51.9
Age at Diagnosis			
< 60	66		50.4
60	65		49.6
Year of Diagnosis			
1994 – 1999	33		25.2
2000 – 2005	52		39.7
2006 – 2010	46		35.1
Surgical Resection			
No	16		12.2
Yes	115		87.8
Radiation Therapy			
No	100		76.3
Yes	31		23.7
Chemotherapy			
No	94		71.8
Yes	37		28.2
Metastasis at Presentation			
No	108		82.4
Yes	23		17.6
Mets and Surgery			
No	9		39.1
Yes	14		60.9
Metastatectomy*			
No	7		50.0
Yes	7		50.0
Surgical Resection Margins			
R0	36		31.3
R1	56		48.7
R2	18		15.7
Unknown	5		4.30
Tumor size			

Variable (n)	Number	%	Percent
< 5 cm	9		6.87
5 – 15 cm	62		47.3
> 15 cm	60		45.8
Grade			
Low	23		17.6
Moderate	27		20.6
High	69		52.7
Unknown	12		9.16
Number of Organs Resected			
0	21		18.3
1–2	59		51.3
3–4	27		23.5
5	8		6.96
Organ Resected			
IVC	18		
Kidney	51		
Colon	25		
Pancreas	15		
Whipple	8		
Diaphragm	5		
Spleen	11		
Histology			
WDLPS	18		13.5
DDLPS	32		24.4
Leiomyosarcoma	52		39.7
MPNST	5		3.80
Angiosarcoma	4		3.00
Synovial Cell Sarcoma	4		3.00
MSFT	3		2.30
Myxoid liposarcoma	1		0.75
Rhabdomyosarcoma	1		0.75
Fibrosarcoma	1		0.75
Sarcoma NOS	10		7.6

* Metastatectomy performed in patients with metastases who underwent surgery

WDLPS – Well Differentiated Liposarcoma; DDLPS – DeDifferentiated Liposarcoma MPNST – Malignant peripheral nerve sheath tumor; MSFT – Malignant Solitary Fibrous Tumor

Table 2

Overall Survival

Variable	Multivariate Adjusted HR (All Patients n = 131) 5% HR 95%	p-value	Multivariate Adjusted HR (Surgical Patients n = 115) 5% HR 95%	p-value
Gender				
Female	<i>Referent</i>		<i>Referent</i>	
Male	1.16 2.00 3.45	0.012	1.47 2.76 5.18	0.002
Age at Surgery				
<60 years	<i>Referent</i>		<i>Referent</i>	
>60 years	1.19 2.00 3.34	0.009	1.41 2.61 4.84	0.002
Metastasis				
No	<i>Referent</i>		<i>Referent</i>	
Yes	2.19 4.50 9.23	<0.001	1.88 4.79 12.2	0.001
Surgery				
R0 Resection	<i>Referent</i>		<i>Referent</i>	
R1 Resection	0.54 1.02 1.94	0.943	0.62 1.23 2.46	0.553
R2 Resection	2.80 6.51 15.1	<0.001	2.73 6.66 16.2	<0.001
Unknown (R0 or R1)	0.51 1.65 5.29	0.402	0.59 1.92 6.23	0.277
No Resection	3.24 8.24 21.0	<0.001		
Radiation				
No	<i>Referent</i>		<i>Referent</i>	
Yes	0.28 0.53 0.99	0.046	0.28 0.57 1.16	0.122
Chemotherapy				
No	<i>Referent</i>		<i>Referent</i>	
Yes	0.38 0.75 1.48	0.408	0.39 0.91 2.10	0.824
Tumor Size				
<5 cm	<i>Referent</i>		<i>Referent</i>	
5 – 15 cm	0.48 1.32 3.66	0.595	0.36 1.17 3.75	0.789
>15 cm	0.66 1.74 4.59	0.265	0.61 1.85 5.61	0.277
Histology				
WDLPS	<i>Referent</i>		<i>Referent</i>	
DDLPS	0.70 2.04 5.93	0.190	0.66 2.02 6.21	0.221
LMS	0.64 1.90 5.62	0.246	0.72 2.52 8.86	0.148
Other	0.73 2.34 7.55	0.154	0.65 2.63 10.6	0.174
Grade				
Low/Intermediate	<i>Referent</i>		<i>Referent</i>	
High	1.24 2.20 3.87	0.007	1.06 2.01 3.79	0.032

Variable	Multivariate Adjusted HR (All Patients n = 131) 5% HR 95%	p-value	Multivariate Adjusted HR (Surgical Patients n = 115) 5% HR 95%	p-value
Unknown	0.87 2.24 5.80	0.096	0.49 1.76 6.32	0.389
Number of Organs Resected				
0			<i>Referent</i>	
1–2			0.55 1.37 3.43	0.498
3–4			0.43 1.16 3.10	0.770
5			1.73 6.25 22.6	0.005

WDLPS - Well Differentiated Liposarcoma, DDLPS - Dedifferentiated Liposarcoma, LMS - Leiomyosarcoma

Table 3

Overall Recurrence (n = 87)

Variable	Multivariate Adjusted Hazard Ratio	p-value
Gender		
Female	<i>Referent</i>	
Male	0.98 1.83 3.40	0.055
Age at Surgery		
<60 years	<i>Referent</i>	
>60 years	0.65 1.17 2.10	0.603
Metastasis		
No	<i>Referent</i>	
Yes	1.92 6.61 22.8	0.003
Surgery		
R0 Resection	<i>Referent</i>	
R1 Resection	2.01 4.28 9.09	<0.001
Unknown (R0 or R1)	0.28 0.95 3.21	0.935
Radiation		
No	<i>Referent</i>	
Yes	0.61 1.25 2.59	0.538
Chemotherapy		
No	<i>Referent</i>	
Yes	0.52 1.24 2.93	0.630
Tumor Size		
<5 cm	<i>Referent</i>	
5 – 15 cm	0.40 1.48 _{5.54}	0.558
>15 cm	1.21 4.38 15.8	0.024
Histology		
WDLPS	<i>Referent</i>	
DDLPS	0.42 1.18 3.35	0.755
LMS	1.26 4.09 13.3	0.019
Other	1.38 5.17 19.3	0.015
Grade		
Low/Intermediate	<i>Referent</i>	
High	0.96 1.85 3.57	0.066
Unknown	0.61 2.11 7.34	0.241
Number of Organs Resected		

Variable	Multivariate Adjusted Hazard Ratio	p-value
0	<i>Referent</i>	
1–2	0.85 2.33 6.40	0.101
3–4	0.69 1.83 4.83	0.222
5	3.77 17.8 84.5	<0.001

WDLPS - Well Differentiated Liposarcoma, DDLPS - Dedifferentiated Liposarcoma, LMS - Leiomyosarcoma

Table 4

Local Recurrence (n = 87)

Variable	Multivariate Adjusted Hazard Ratio	p-value
Gender		
Female	<i>Referent</i>	
Male	0.55 1.10 2.23	0.793
Age at Surgery		
<60 years	<i>Referent</i>	
>60 years	0.67 1.36 2.79	0.393
Surgery		
R0 Resection	<i>Referent</i>	
R1 Resection	1.45 3.82 10.0	0.006
Unknown (R0 or R1)	0.27 1.40 7.23	0.685
Radiation		
No	<i>Referent</i>	
Yes	0.09 0.28 0.86	0.026
Tumor Size		
<5 cm	<i>Referent</i>	
5 – 15 cm	0.45 2.39 12.8	0.312
>15 cm	0.91 4.72 24.6	0.066
Histology		
WDLPS	<i>Referent</i>	
DDLPS	0.96 2.50 6.53	0.061
LMS	0.46 1.49 4.81	0.504
Other	1.60 5.73 20.5	0.007
Spleen Resection		
No	<i>Referent</i>	
Yes	0.92 2.87 6.53	0.068
Pancreas Resection		
No	<i>Referent</i>	
Yes	0.60 1.65 4.59	0.336
Diaphragm Resection		
No	<i>Referent</i>	
Yes	2.75 18.5 123	0.003

WDLPS - Well Differentiated Liposarcoma, DDLPS - Dedifferentiated Liposarcoma, LMS - Leiomyosarcoma

Table 5

Distant Recurrence (n = 87)

Variable	Multivariate Adjusted Hazard Ratio	p-value
Gender		
Female	<i>Referent</i>	
Male	1.06 2.31 5.02	0.035
Age at Surgery		
<60 years	<i>Referent</i>	
>60 years	0.61 1.26 2.59	0.527
Mets		
No	<i>Referent</i>	
Yes	1.98 8.09 33.1	0.004
Surgery		
R0 Resection	<i>Referent</i>	
R1 Resection	0.82 1.91 4.43	0.132
Unknown (R0 or R1)	0.11 0.55 2.84	0.475
Chemotherapy		
No	<i>Referent</i>	
Yes	0.47 1.24 3.26	0.669
Tumor Size		
<5 cm	<i>Referent</i>	
5 – 15 cm	0.32 1.35 5.78	0.685
>15 cm	1.14 4.93 21.3	0.032
Histology		
WDLPS	<i>Referent</i>	
DDLPS	1.4 x 10⁹	<0.001
LMS	2.4 x 10¹⁰	<0.001
Other	2.8 x 10¹⁰	<0.001
Grade		
Low/Intermediate	<i>Referent</i>	
High	1.08 2.52 5.88	0.033
Unknown	0.25 1.61 10.4	0.616
IVC		
No	<i>Referent</i>	
Yes	0.48 1.20 2.99	0.695
Diaphragm Resection		

Variable	Multivariate Adjusted Hazard Ratio	p-value
No	<i>Referent</i>	
Yes	1.77 15.1 129	0.013

WDLPS - Well Differentiated Liposarcoma, DDLPS - Dedifferentiated Liposarcoma, LMS - Leiomyosarcoma