Operative Management of Primary Retroperitoneal Sarcomas

A Reappraisal of an Institutional Experience

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Objective: To review our recent experience with primary retroperitoneal sarcomas, determine prognostic factors for disease recurrence and patient survival, and compare them to our previous results.

Background: Medical therapies have shown little efficacy in the management of retroperitoneal sarcomas, making total surgical extirpation the best chance for patient cure.

Methods: The case histories of all patients operated upon for retroperitoneal sarcomas between January 1983 and December 1995 were retrospectively reviewed.

Results: Ninety-seven patients underwent attempted surgical resection of a primary retroperitoneal sarcoma. There were 54 (56%) men and 43 (44%) women, with a mean age of 59 years. Seventy-six (78%) patients underwent gross total resection, 13 (14%) had residual disease, and 8 (8%) underwent biopsy only with an actuarial 1-year survival of 88%, 51%, and 47%, respectively ($P = 0.001$). The actuarial 5- and 10-year survivals for patients who underwent gross total resection were 51% and 36%, respectively. Thirty-three patients (43%) developed locoregional recurrence, and 20 patients (26%) developed distant metastases at a median time of 12 months. The cumulative probability at 5 years was 44% for locoregional recurrence and 29% for distant metastases. On univariate analysis, factors associated with improved survival were complete resection of the tumor ($P = 0.001$), nonmetastatic disease at presentation ($P = 0.01$), low-grade tumors ($P = 0.02$), liposarcomas ($P = 0.003$), and no disease recurrence ($P = 0.0001$). Contrary to previous reports, the histologic subtype ($P = 0.04$) was the only significant factor predicting survival on multivariate analysis.

Conclusions: Compared with our earlier experience, the rates of complete resection and overall survival have improved. Local control continues to be a significant problem in the management of retroperitoneal sarcomas. Because new surgical options for this problem are limited, further outcome improvement requires novel adjuvant therapies.

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Retroperitoneal sarcomas are rare malignancies with an estimated incidence of 1000 cases per year in the United States.[1] Medical therapies have shown little efficacy, making total surgical extirpation the only chance for patient cure.[2] Because of the lack of distinct anatomic compartments in the retroperitoneum, these invasive neoplasms often grow to a large size and involve multiple adjacent structures before diagnosis.[3] This propensity poses a challenge for the surgeon to achieve a safe and microscopically complete tumor resection. Despite advances in diagnostic modalities, surgical techniques and the adaptation of more aggressive procedures, this disease still has a propensity for local recurrence, even after an apparent complete resection.[4] The current prognoses of patients with these tumors remain guarded, with an overall 5-year patient survival of 15–30%.[5,6,7] Local disease recurrence remains the main cause of mortality.

We previously reported our institution's experience with the management of retroperitoneal sarcomas.[7] That 20-year experience (1960–1983) before the advent of routine computerized tomography (CT) imaging identified clinical, pathologic, and treatment variables that were associated with tumor recurrence and patient outcome. We herein report our experience during the subsequent 13 years (1983–1995).

MATERIALS AND METHODS

From January 1983 to December 1995, 97 patients underwent surgical exploration at our institution for a primary retroperitoneal sarcoma. Patients with recurrent sarcomas, patients with sarcomas originating from the gastrointestinal

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and genitourinary tracts, and patients with sarcomas below the age of 16 years were excluded. Patient histories including the surgeon's operative note, hospital records, and follow-up data were reviewed for the following variables: patient age, gender, presenting symptoms and duration, type of operation (classified as: biopsy alone, incomplete resection, or gross total resection), tumor grade, histologic type, maximum tumor diameter and involvement of normal structures, regional lymph node involvement, distant metastases, and the administration of preoperative, intraoperative, and postoperative radiation and chemotherapy. Both univariate and multivariate analyses were performed to determine which risk factors were significantly associated with tumor recurrence and death from disease. Survival and recurrence rates were compared between the current study group and our previously reported cohort of patients.

Surgical resection was considered complete if all macroscopic disease was removed and no microscopic margin involvement was noted. Exhaustive attempts to obtain microscopically negative margins of large tumors were not routinely pursued. The resection was considered incomplete if either gross or presumed microscopic residual disease was present at the end of the operation. Initially 108 patients were identified with retroperitoneal sarcomas on the basis of the initial postoperative pathology; however, on rereview of pathology specimens, eleven patients were excluded because they were found to have histology other than that of retroperitoneal sarcoma. If possible, patients were routinely followed with CT scans every 3 months for the first year, every 4 months for the second year, and yearly thereafter.

In analyzing for tumor recurrence and patient death, grade 1 (low-grade) sarcomas were distinguished from high-grade sarcomas (grades 2–4). Tumors were staged according to the American Joint Committee on Cancer (AJCC) 1997 fifth edition staging system.[8]

Patient survival and disease-free survivals were calculated using the Kaplan-Meier method.[9] Clinical, treatment, and pathologic variables were evaluated with log-rank test[10] and Cox's proportionate hazard models[11] to identify factors associated with recurrence and death.

RESULTS

Patient Presentation

There were 54 men (56%) and 43 women (44%), with a mean age of 59 years (range, 16–83 years). Symptoms were documented preoperatively in 79 patients (81%), whereas 18 patients (19%) were asymptomatic with the tumor discovered incidentally during evaluation for an unrelated problem. The mean duration of symptoms prior to surgery was 5 months (median, 2 months; range, 0–60 months). The majority of patients (61%) presented with multiple signs and symptoms. Pain (57%), abdominal mass (36%) or distension (25%), nonspecific gastrointestinal complaints (26%), and weight loss (29%) were the most commonly documented presenting signs and symptoms.

Operative Management

Gross total resection was possible in 76 (78%) of the patients, 13 (14%) patients underwent incomplete extirpation, and 8 (8%) patients had only a surgical biopsy. Adjacent organs were resected en bloc with the tumor in 48 (63%) of the 76 patients who underwent gross total resection. More than one organ was resected in 22 patients. Among the 13 patients who had residual disease after resection, 8 (62%) patients also had resection of one or more adjacent organs. The kidney was the most frequently resected organ, followed by segmental resection of the large bowel, spleen, and pancreas (Table 1).

Morbidity and Mortality

There were 2 postoperative deaths. One patient died of pulmonary embolization and the second from multiorgan failure following intraoperative hemorrhage. Additional major postoperative complications occurred in 7 patients (8%) and required reoperation in 6. These complications included postoperative hemorrhage, abdominal abscess, acalculous cholecystitis, enterocutaneous fistula, external iliac artery thrombosis, and external iliac artery interposition graft thrombosis in one patient each. The seventh patient who developed an intraabdominal abscess was managed by CT-guided drainage.

Pathologic Characteristics and Stage of Tumor at Operation

Leiomyosarcomas, liposarcomas, and malignant fibrous histiocytomas (MFH) together constituted 90% of the tumors (Table 2). Ninety-four tumors (97%) were >5 cm or were attached to adjacent structures. The majority (79%) of these were high-grade sarcomas (G2-4) (Table 3). Eleven patients (12%) had distant metastases at the time of their initial operation, including 6 patients with peritoneal metastases who underwent gross total resection of the primary

TABLE 1. Frequency of Adjacent Organs Resected During Primary Retroperitoneal Sarcoma Resections

Organ	No. (%) of Patients
Kidney	35 (36)
Colon	21 (22)
Spleen	10 (10)
Pancreas	9 (9)
Small intestine	6 (6)
Stomach	6 (6)
Inferior vena cava	3 (3)

TABLE 2. Histologic Subtypes of Retroperitoneal Sarcomas

Histologic Type	No. (%) of Patients
Liposarcoma	53 (55)
Leiomyosarcoma	25 (26)
Malignant fibrous histiocytoma	10 (10)
Fibrosarcoma	5 (5)
Malignant peripheral nerve sheath tumor	3 (3)
Extraskeletal osteosarcoma	1 (1)

tumor and metastatic disease at the same time. Peritoneal (7 patients), lung (2 patients), and osseous (2 patients) were the sites of metastatic disease at initial presentation.

Overall Survival

Complete resection of the primary tumor was associated with a significantly better survival (88% 1-year actuarial survival) compared with incomplete resection or a biopsy only ($P = 0.001$) (Fig. 1). Patients who underwent only a biopsy (n = 8) or incomplete resection of tumor (n = 13) had actuarial 1-year survivals of 47% (95% CI, 22–100) and 51% (95% CI, 30–89), respectively. Using univariate analysis, factors associated with improved survival in patients who underwent gross total resection included nonmetastatic sarcoma at presentation ($P = 0.01$), low-grade sarcomas ($P = 0.02$), stage II ($P = 0.01$), and liposarcoma ($P = 0.003$). In the multivariate analysis, however, only leiomyosarcoma was an independent variable predicting poor survival. Patients with leiomyosarcomas were twice as likely to die of disease as those with liposarcomas ($P = 0.002$) (Fig. 2). In a time-dependent analysis with a Cox proportional hazard model, patients with local recurrence were 4.6 times more likely to die than patients who did not develop a local recurrence ($P = 0.0001$), and patients with distant metastases were 5 times ($P = 0.0001$) more likely to die than patients who did not develop distant metastases.

TABLE 3. Tumor Staging of Retroperitoneal Sarcomas

	No. (%) of Patients
Stage	
I	0
II	11 (12)
III	24 (24)
IV	62 (64)
Grade	
G1	20 (21)
G2	10 (10)
G3	20 (21)
G4	47 (48)
Tumor	
T1 (≤5 cm)	3 (3)
T2 (>5 cm)	94 (97)
Nodes	
N0	96 (99)
N1	1 (1)
Metastasis	
M0	86 (89)
M1	11 (11)

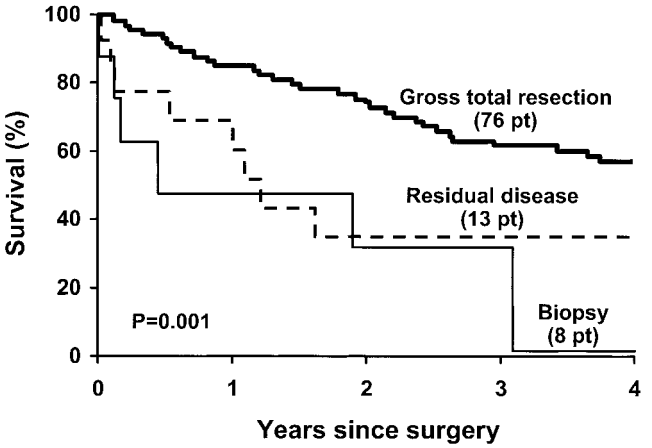

FIGURE 1. Survival curves of patients by type of operation. Patients undergoing complete resection (n = 76) had a better survival as compared with patients with incomplete resection (n = 13) or biopsy (n = 8); $P = 0.001$.

Recurrent Disease

The median follow-up for all patients was 3 years, and median follow-up for survivors was 6 years. Of the 76

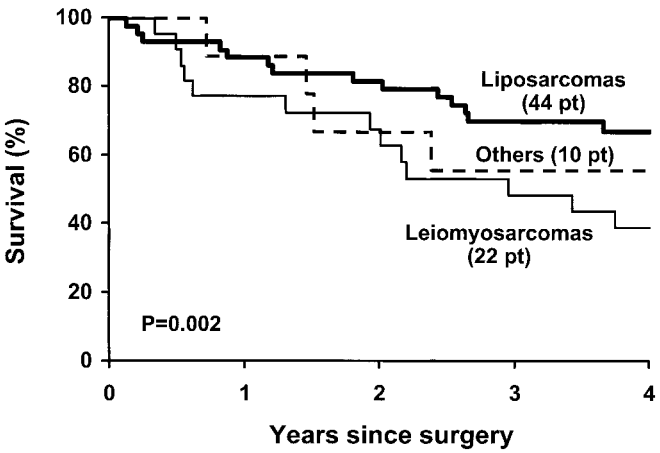

FIGURE 2. Survival curves of patients by histologic subtype. Patients with leiomyosarcomas (n = 22) had a worse survival as compared with patients with liposarcomas (n = 44); $P = 0.0001$.

patients who underwent gross total resection, 43 patients (57%) developed locoregional recurrence or metastatic disease. Thirty-three patients (43%) developed locoregional recurrence, including 10 with synchronous distant metastases (3 peritoneal, 2 hepatic, 2 pulmonary, 2 hepatic and pulmonary, and 1 with pulmonary and osseous metastases). Ten patients (14%) developed only distant metastases (4 hepatic, 3 osseous, 1 pulmonary, 1 with both hepatic and pulmonary disease, and 1 with both hepatic and peritoneal disease). The cumulative 5-year probability for local recurrence was 44% (95% CI, 22–45), for distant metastases was 29% (95% CI, 5–26) and for both local and distant recurrence was 15% (95% CI, 5–26).

Histologic subtype was a significant predictor for the development of metastatic disease, but not for local recurrence by univariate analysis model. The 5-year probability of local recurrence was 44% for liposarcomas and 40% for leiomyosarcomas [95% CI, 26–59 ($P = 0.87$)]. In contrast, the 5-year probability of distant metastases was 13% for liposarcomas but 44% for leiomyosarcomas [95% CI, 14–62 ($P = 0.0001$)]. Other tumor characteristics, including diameter, stage, and histologic grade, had no significant impact on the risk for either local recurrence or distant metastases.

Surgical Management of Recurrent Disease

Among the 43 patients who developed local recurrence, metastatic disease, or both, 24 patients underwent a second operation to resect all recurrent tumor. Gross total resection of the recurrent sarcoma was possible in 15 (62%) of these patients, 5 patients (21%) underwent incomplete extirpation, and 4 patients (16%) had only a surgical biopsy. Patients with local recurrence alone (12 of 23, 48%) were more likely to be amenable to complete resection of their recurrent disease compared with patients with distant metastases alone, 1 of 10 (one patient with liver metastasis, 10%), or both local and distant sites of failure, 2 of 10 (one patient with liver metastasis and one patient with liver and lung metastases, 20%). The grade and histologic subtype of recurrent sarcomas were comparable to the original tumors.

Among those patients who underwent a gross total resection of their first recurrence, 7 patients (47%) developed a second recurrence and 6 (86%) had gross total resection of disease a second time. There was a significant improvement in the survival of patients with recurrent sarcoma amenable to complete resection compared with those that did not undergo resection or had incomplete resection [1-year survival: 83% (95% CI, 69–99) with complete resection and 32% (95% CI, 16–/61) without total excision of disease ($P = 0.0001$)] (Fig. 3).

Symptomatic recurrences occurred in 10 patients. Symptoms of local recurrence included abdominal distension and pain in 7 patients; fever and fatigue, hemorrhage, and a small bowel obstruction occurred in one patient each. All 10 of these patients had operative treatment of their symptomatic

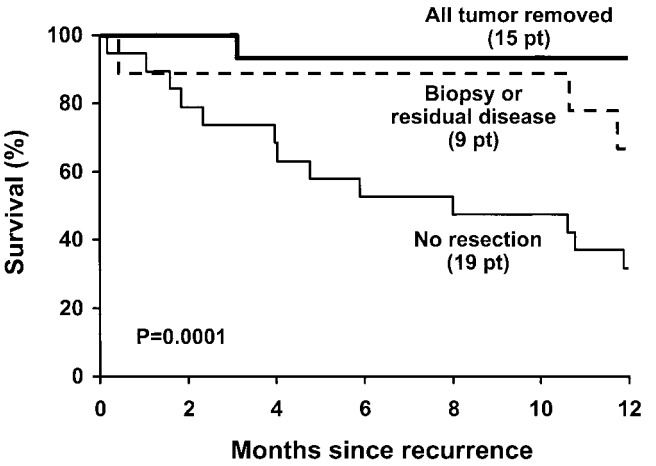

FIGURE 3. Survival curves of patients who developed recurrence after complete resection. Patients who underwent complete resection (n=15) of their recurrence had a better survival as compared with those who residual disease or biopsy only (n=9) or no resection at all (n=19), $P = 0.001$).

recurrence. Improvement of symptoms occurred in 60% of these patients. For asymptomatic patients (n = 33), CT was the most common method (90%) of detection for both local recurrence and metastatic disease followed by physical examination (10%). There was no difference in survival between patients with symptomatic or asymptomatic recurrences.

Adjuvant Therapy

Thirty-seven patients (49%) who had complete tumor resection received adjuvant radiation therapy. This included preoperative external beam radiation therapy in 16 patients (43%), intraoperative radiation in 11 patients (28%), and postoperative radiation in 16 patients (43%). Adjuvant radiation therapy was not associated with a higher incidence of complications.

Preoperative, intraoperative, or postoperative radiation therapy alone or in any combination did not significantly decrease local recurrence rates or improve patient survival. The probability of disease recurrence at 5 years was 41% (95% CI, 11–53) with adjuvant radiation and 45% (95% CI, 15–46) without adjuvant radiation therapy ($P = 0.76$). Thirteen patients (17%) received adjuvant chemotherapy, a factor associated with poorer patient survival. Actuarial 5-year survival was 17% (95% CI, 30–67) with adjuvant chemotherapy and 58% (95% CI, 41–73) ($P = 0.001$) without adjuvant chemotherapy. Patients with lieyomyosarcomas were more likely to receive chemotherapy ($P = 0.03$) and radiation therapy ($P = 0.01$) than patients with liposarcomas.

Comparison With Previous Mayo Clinic Data (1960–1982)

The gender and age of patients presenting for initial treatment of their retroperitoneal sarcoma were the same

between the 2 study populations. There were more asymptomatic patients (18% versus 2%, $P = 0.001$), and the median duration of symptoms was shorter (2 versus 3.5 months, $P = 0.01$) in the current cohort of patients. The prevalences of presenting symptoms were similar between the 2 study periods; however, patients were less likely to present with a palpable mass (36%) than in the earlier group (67%, $P = 0.001$). Tumor grade, mean tumor diameter, and involvement of other structures, histologic types, and incidence of nodal involvement were similar, but fewer patients had metastatic disease at presentation in our current study cohort (9% versus 22%, $P = 0.014$) than in the earlier patient population.

The later cohort of patients was more likely to have complete tumor resection (78% versus 49%, $P = 0.001$) and less likely to undergo only biopsy (8% versus 28%, $P = 0.001$). There was a significant difference between the percentage of patients having adherent organs resected (58% of the patients in the current series versus 39% previously, $P = 0.009$). While no statistically significant difference in the probability of local recurrence rates at 5 years was noted (29% versus 42%, $P = 0.133$), there was a trend toward fewer recurrences. The more recent study cohort was noted to have a higher incidence of distant recurrence at 5 years (15% versus 0%, $P = 0.002$).

The overall 5- and 10-year survival rates for patients undergoing initial surgical resection of primary retroperitoneal sarcomas were significantly better in our more recent experience (45% and 29%) compared with the previous study period (34% and 19%) ($P = 0.01$) (Fig. 4). Also the 5- and 10-year survival rates for patients undergoing gross total resection of their tumors were improved in our current experience (51% and 36%) compared with the prior cohort of patients (46% and 33%) ($P = 0.043$).

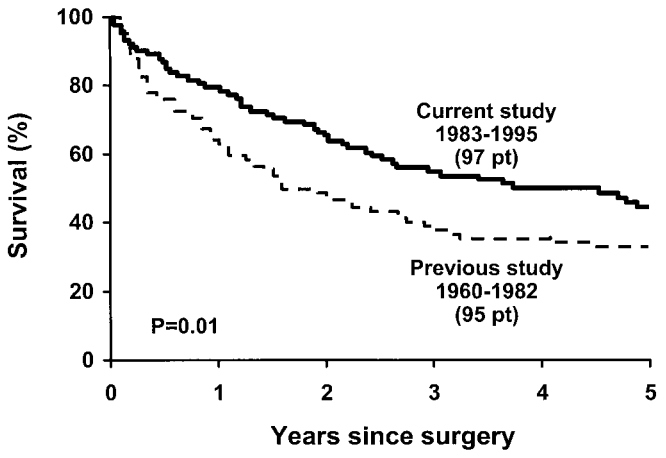

FIGURE 4. Survival curves of patients who underwent attempted resection of primary retroperitoneal sarcomas between 1960–1982 (n = 95 patients) and 1983–1995 (n = 97 patients) at the Mayo Clinic.

DISCUSSION

This report comparing our operative experience with retroperitoneal sarcomas between 2 time periods highlights advances made in the management of these cancers, as well as the continuing challenges faced by clinicians who treat this formidable disease. The increased incidence of asymptomatic patients and the earlier detection of tumor in symptomatic patients in our more recent experience reflect the increased use of CT scanning as a diagnostic tool by the medical profession. Despite the increased use of CT scans, most retroperitoneal sarcomas are still detected as locally advanced tumors. Ninety-seven percent of our patients had tumors > 5 cm or involving adjacent organs at the time of diagnosis. Delay in tumor detection is due to the lack of pain with small retroperitoneal masses, allowing a sarcoma to grow to a large size before diagnosis.

The percentage of completely resectable retroperitoneal sarcomas significantly increased from 49% in 1960–1982 to 78% in 1983–1995. Our current rates are comparable to those recently reported from other major cancer centers.[3,5,12–14] The tumor characteristics, including stage at presentation, histologic subtype, grade, and size, have not significantly changed between the 2 time periods of our experience.

Completeness of tumor resection correlated with patient survival as noted by multiple previous experiences.[2,3,7,12–16] Patients undergoing complete resection of their tumor had a significantly better outcome than those who had residual disease. In our experience, resection was deemed complete if the macroscopic margins were negative. In the retroperitoneum, with no definite anatomic boundaries and large tumor size, the determination of negative microscopic margins is a difficult and imprecise task. With the comparable local recurrence rates in our present experience and other reports,[12,13,17] distinction between gross tumor excision and microscopic negative margins does not seem to be significant.

Multivariate analysis of variables associated with improved patient survival after complete resection revealed only the histologic subtype to be an independent predictor of outcome. This contradicts several other reported series,[3,7,12–14] which found grade as the most important predictor of survival in patients with retroperitoneal sarcomas**.** In our experience, while the number of completely resected high-grade liposarcomas and leiomyosarcomas was similar, the incidence of distant metastasis was significantly higher for leiomyosarcomas and was associated with a poor outcome. This would suggest that leiomyosarcomas are inherently more aggressive tumors, accounting for the decreased survival associated with them. In another report[16] of retroperitoneal sarcomas that did not show grade to be a significant predictor of survival, Heslin[16] felt this finding resulted from high-grade tumors having an early impact on patient mortality, but high grade tumors that did not metastasize or

locally recur early were biologically less aggressive and therefore did not have any greater impact on survival compared with low-grade sarcomas with extended follow-up.

Local recurrence alone occurred in one third of the patients (23 of 76) undergoing complete sarcoma resection. This event was a predictor of a poor outcome compared with patients without disease recurrence. Our data confirm the predisposition of retroperitoneal sarcomas to recur despite an apparent adequate surgical resection. Several other authors[7,11–16] have demonstrated these findings. Among the patients who developed locally recurrent sarcoma, almost half were amenable to a second complete tumor resection. The patients who had a complete resection of their recurrent disease had a better mean survival compared with patients who did not have complete resection of their disease recurrence. While patients who underwent a biopsy or an incomplete resection of their recurrence had an initial survival comparable those with a complete resection, this did not persist after longer follow-up. These results are similar to others reports[13,14,16] and support an aggressive surgical approach to patients with recurrent disease if complete resection appears feasible after preoperative evaluation.

The increased incidence of metastatic disease in our later patient cohort is probably due in part to better detection methods (ie, CT scans) for asymptomatic metastases and improved patient follow-up. Metastatic disease at the time of presentation, although uncommon, was associated with a significantly worse prognosis. Traditionally patients with retroperitoneal sarcomas have been described as being more likely to die of local recurrence rather than distant metastasis.[7,14] This was due in part to the fact that the prevalence of local recurrence was more common than distant metastases. In our more recent patient cohort, 26% of all the patients undergoing gross total resection developed metastatic disease and all died of disease. The incidence of metastatic disease alone or with local recurrence is not insignificant, particularly in patients with leiomyosarcomas, and represents an almost universally lethal event when it occurs.

The resectability and survival rates between patients who had asymptomatic recurrences detected by CT scan and patients with symptomatic recurrences were similar. Despite this fact, because of the significant probability of local and distant tumor recurrence during the first 2 years postoperatively and the improved survival with complete resection of recurrent disease, we believe frequent follow up is justifiable for all patients undergoing a gross total resection. A CT scan every 3–4 months for the first 2 years, followed by less frequent examinations for 3–5 years and annually thereafter is recommended. The propensity of these tumors to recur even after 10 years should also warrant life long follow-up; however, whether this protocol actually translates to increased resectability and improved survival remains to be proven.

We were unable to demonstrate a favorable impact of radiation therapy on local and distant disease recurrence rates or overall patient survival, as have several previous authors.[2,3,5,13–15] The only randomized trial evaluating radiation therapy in the management of retroperitoneal sarcomas by Sindelar et al[18] compared intraoperative and low-dose postoperative radiation to high-dose postoperative radiation. Patients in the intraoperative radiation therapy arm had significantly better local disease control but did not have better overall survival. Several uncontrolled experiences with retroperitoneal sarcoma patients[17,19,20,21] have suggested survival benefit with adjuvant radiation therapy. Data from uncontrolled trials[22–24] and 2 randomized trials[25,26] for soft tissue sarcomas of the extremities have demonstrated better local control and survival with external beam radiation therapy (EBRT) plus resection compared with surgical therapy alone. Despite a paucity of controlled trials confirming the efficacy of radiation therapy in retroperitoneal sarcomas, we feel adjuvant radiation may still play a role in improving local disease control and potentially patient survival.

Studies[19,27] have suggested that the probability of local control increases with escalation of radiation dose. However dose escalation with postoperative radiation must be limited because of the radiation tolerance of normal tissues, including loops of bowel fixed by postoperative adhesions.[28] In these situations, preoperative radiation is an attractive option, since normal intervening organs are displaced by the tumor, allowing for higher doses of radiation to be used.

Several authors have advocated the use of intraoperative radiotherapy (IORT), as it circumvents some of the limitations of preoperative and postoperative EBRT.[18,29,30,31] The only randomized trial looking at IORT as an adjuvant treatment modality showed improvement in local control, but it could not detect an increase in patient survival.[18] Petersen et al[30] have reported a estimated 5-year local control of 58% after a median follow-up of 3 years in 87 patients who were treated with IORT, plus external beam radiation. The optimal treatment strategy for local tumor control may require a combination of surgery and radiation, but further trials are necessary to determine the best combination.

One fifth of the patients in our current study received some form of chemotherapy. Their survival was worse, likely as a result of chemotherapy being reserved for patients with poor prognostic factors, including metastatic disease, leiomyosarcomas, and high-grade tumors. The observation has been made by others[5,7,16,32] as there have been no reports of effective conventional chemotherapy in the treatment of retroperitoneal sarcomas.

Our current 5- and 10-year survival rates improved significantly compared with our previous experience. A combination of (1) increased use of extensive resection with en bloc removal of adjacent organs, (2) a lower incidence of local recurrence, and (3) more attempts at complete resection

of recurrent sarcomas likely account for this outcome. Our recent rates of local disease recurrence, distant metastases, and overall survival are comparable to reports from other major centers,[3,5,12–14] confirming that an aggressive surgical technique with *en-bloc* resection is crucial for the successful management of retroperitoneal sarcomas. However, while the best outcomes occur when patients undergo total surgical resection, the highly lethal nature of local and distant sarcoma recurrence, makes improved adjuvant therapy a critical need.

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