

Retroperitoneal Soft-Tissue Sarcoma

Analysis of 500 Patients Treated and Followed at a Single Institution

Jonathan J. Lewis, MD, PhD,* Denis Leung, PhD,† James M. Woodruff, MD,‡ and Murray F. Brennan, MD*

From the Departments of Surgery,* Biostatistics,† and Pathology,‡ Memorial Sloan-Kettering Cancer Center, New York City, New York

Objective

To analyze treatment and survival of a large cohort of patients with retroperitoneal soft-tissue sarcomas (STS) treated and prospectively followed at a single institution.

Summary Background Data

Retroperitoneal STS are relatively uncommon and constitute a difficult management problem. Although surgical resection is often difficult or impossible, current chemotherapy is not effective and radiation is limited by toxicity to adjacent structures. Thus, complete surgical resection remains the most effective modality for selected primary and recurrent disease.

Methods

Five hundred patients with retroperitoneal STS were admitted and treated between July 1, 1982, and September 30, 1997, and prospectively followed. Patient, tumor, and treatment variables were analyzed for disease-specific and disease-free survival. Survival was determined with the Kaplan-Meier method. Statistical significance was evaluated using the log-

rank test for univariate influence and Cox model stepwise regression for multivariate influence.

Results

Two hundred seventy-eight patients (56%) had primary disease and 222 (44%) recurrent disease. Median follow-up was 28 months (range 1 to 172 months), 40 months for survivors. Median survival was 72 months for patients with primary disease, 28 months for those with local recurrence, and 10 months for those with metastasis. For patients with primary or locally recurrent tumors, unresectable disease, incomplete resection, and high-grade tumors significantly reduced survival time.

Conclusions

In this study of patients with retroperitoneal STS, stage at presentation, high histologic grade, unresectable primary tumor, and positive gross margin are strongly associated with the tumor mortality rate. Patients approached with curative intent should undergo aggressive attempts at complete surgical resection. Incomplete resection should be undertaken only for symptom relief.

Retroperitoneal soft-tissue sarcomas (STS) are relatively uncommon and constitute a difficult management problem.^{1,2} Most tumors in the retroperitoneum are malignant, and about one third of these are STS.^{2,3} The dilemma posed by the biology of these tumors is contingent on the anatomic location, with consequent late presentation and frequent invasion of contiguous retroperitoneal structures. These factors often make surgical resection

difficult or impossible. Current chemotherapy for retroperitoneal STS is not effective, and radiation is limited by toxicity to adjacent intraabdominal structures.⁴ It would therefore seem that complete surgical resection remains the most effective modality for selected primary and recurrent disease.

The aim of this study was to analyze disease-specific survival and disease-free survival in a large, well-characterized cohort of prospectively followed patients with retroperitoneal STS managed at a single institution. In particular, we analyzed the correlation of tumor biology and surgical treatment with subsequent local recurrence, metastasis, and disease-specific survival. The focus was to determine the role of surgical resection in the management of primary and locally recurrent disease.

Presented at the 118th Annual Meeting of the American Surgical Association, Palm Beach, FL, April 1998.

Supported by NIH Grant CA-47179.

Address reprint requests to Jonathan J. Lewis, MD, PhD, Department of Surgery, Memorial Sloan-Kettering Cancer Center, 1275 York Ave., New York, NY 10021

Accepted for publication April 1998.

METHODS

Patients

A prospective data base of adult patients (older than 16 years) with STS treated at Memorial Sloan-Kettering Cancer Center (MSKCC) was established in July 1982. Patients who underwent treatment for retroperitoneal STS from July 1, 1982, through September 30, 1997, were the subject of this study. Patient, tumor, and treatment variables were correlated with survival endpoints. Patient variables analyzed included age at diagnosis (younger or older than 50 years), sex, and presenting status. Tumor variables analyzed included size (<5, 5 to 10, or >10 cm), histologic grade (low or high), and histologic subtype. Histologic grade was divided into low or high, distinct from other aspects of intermediate transition.^{5,6} Treatment variables analyzed included complete *versus* incomplete resection (*i.e.*, gross margins) and microscopic margins (negative or positive). Because adjuvant radiation or chemotherapy was not prospectively randomized but included both patients prospectively treated in trials and those given standard of care based on prognosis,¹ the inclusion of these variables in any of the analyses would confound the effects of other factors. Therefore, although we report these treatment data, we have chosen not to include them in any of the analyses.

Statistical Analysis

Local recurrence, distant metastasis, and disease-specific survival were used as endpoints of the study. The rates of these endpoints were modeled by the method of Kaplan and Meier.⁷ Local recurrence was defined as the first recurrence of the disease at the site of primary tumor, of the same histologic subtype, occurring more than 3 months after primary therapy. Distant metastasis was defined as recurrence of disease at a distant site either within the abdomen or extraabdominal. Multiple intraabdominal discontinuous recurrence was defined as metastatic. Deaths that were confirmed to be caused by the disease were treated as an endpoint for disease-specific survival; other deaths were treated as censored observations. Disease-specific survival after local or metastatic recurrence was defined as time from first recurrence to time of last follow-up or death. For endpoint times to an event, admission dates were used. Patient, tumor, and treatment factors were correlated to each other by Fisher's exact test or chi square. The univariate association of factors to survival endpoints was performed with the log-rank test. Independent prognostic values of factors were analyzed with the Cox proportional hazards model. The results of the Cox model analysis are reported with relative risks (RR) and confidence intervals (CI). In all statistical analyses, $p < 0.05$ was considered significant.

Table 1. OVERALL PATIENT, TUMOR, PATHOLOGIC CHARACTERISTICS, AND DISTRIBUTION OF EVENTS IN 500 PATIENTS WITH RETROPERITONEAL SARCOMA

	n	% of Total
Presentation status		
Primary	278	56
Local recurrence	119	24
Metastasis	103	20
Sex		
Male	286	57
Female	214	43
Age		
>50 years	329	66
<50 years	171	34
Grade		
High	319	64
Low	181	36
Size		
>10 cm	301	60
<5, >10 cm	123	25
<5 cm	28	6
Unknown	48	9
Histological subtype		
Liposarcoma	206	41
Leiomyosarcoma	133	27
Others	72	14
MFH	33	7
Fibrosarcoma	30	6
Hemangiopericytoma	13	3
MPNT	13	3
Surgical resection margins		
Negative micro & gross margins	209	42
Unresectable	116	23
Positive micro & gross margins	90	18
Positive micro & negative gross margins	85	17
Local recurrence		
No	394	79
Yes	106	21
Distant metastases		
No	454	91
Yes	46	9
Synchronous disease		
No	490	98
Yes	10	2
Survival status		
Died of disease	236	47
Alive	233	47
Died of other causes	31	6

MFH = malignant fibrous histiocytoma; MPNT = malignant peritoneal nerve tumor.

RESULTS

Patients, Tumors, and Treatment

During the time period under study, we admitted and treated 500 patients with retroperitoneal STS to MSKCC. The distribution of clinical and pathologic characteristics in these patients is illustrated in Table 1. The median age of

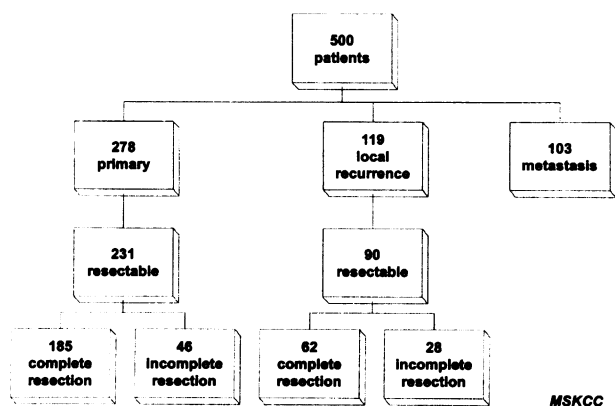


Figure 1. Initial presentation status and surgical pathway of 500 patients with retroperitoneal STS treated at MSKCC from July 1982 through September 1997.

All patients underwent evaluation for resection of primary or recurrent disease whenever possible. In those with primary disease, 231 (83%) underwent resection. Of these, 185 (80%) underwent complete resection. In contrast, in patients whose first presentation to MSKCC was with local recurrence, only 62 patients (52%) underwent complete resection. Sites of first metastasis in the 103 patients with metastasis included the lung in 39 (38%), the liver in 45 (44%), and both liver and lung in 19 (18%).

Patients whose disease was unresectable or who had incomplete resections generally underwent chemotherapy or

patients was 58 years (range 16 to 88 years). Two hundred fourteen patients (43%) were women and 286 (57%) were men. Of the 500 patients, 278 (56%) had primary disease, 119 (24%) local recurrence, and 103 (20%) metastasis (Fig. 1). Kaplan–Meier disease-specific survival, grouped by presentation, is depicted in Figure 2. The median follow-up was 22 months overall (40 months for survivors), with a range of 1 through 172 months. Median survival was 72 months for those with primary disease, 28 months for those with local recurrence, and 10 months for those with metastasis.

Most tumors (n = 319, 64%) were high grade, and most (n = 301, 60%) were >10 cm. The most common histologic subtype was liposarcoma (n = 206, 41%), followed by leiomyosarcoma (n = 133, 27%). In contrast to extremity soft tissue sarcoma, MFH or myxofibrosarcoma was rare (n = 33, 6%). Most patients (n = 401, 80%) had an abdominal mass. Other presenting symptoms included neurologic symptoms in the lower extremities (n = 211, 42%) and pain (n = 187, 37%). There was no proportional difference in presentation symptoms between patients with primary or recurrent disease.

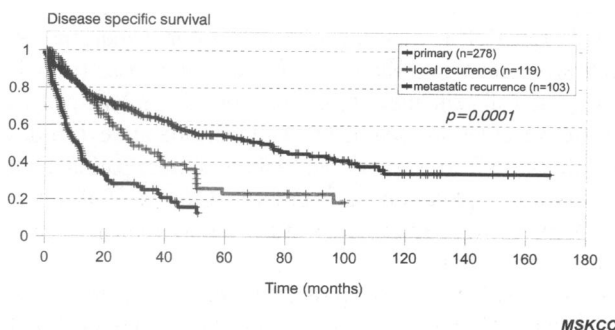


Figure 2. Kaplan–Meier disease-specific survival grouped by presentation status. Of the 500 patients, 278 (56%) had primary disease, 119 (24%) local recurrence, and 103 (20%) metastasis. Median survival was 72 months for those with primary disease, 28 months for those with local recurrence, and 10 months for those with metastasis.

Table 2. PATIENT, TUMOR, PATHOLOGIC CHARACTERISTICS AND DISTRIBUTION OF EVENTS IN 278 PATIENTS PRESENTING WITH PRIMARY DISEASE

	n	% of Total
Sex		
Male	170	61
Female	108	39
Age		
>50 years	183	66
<50 years	95	34
Grade		
High	168	60
Low	110	40
Size		
>10 cm	198	71
<5, >10 cm	63	23
<5 cm	17	6
Histological subtype		
Liposarcoma	116	42
Leiomyosarcoma	63	23
Others	37	13
Fibrosarcoma	22	8
MFH	20	7
Hemangiopericytoma	11	4
MPNT	9	3
Surgical resection margins		
Negative micro & gross margins	136	49
Positive micro & negative gross margins	49	18
Unresectable	47	17
Positive micro & gross margins	46	16
Local recurrence		
No	217	78
Yes	61	22
Distant metastases		
No	248	89
Yes	30	11
Synchronous disease		
No	271	97
Yes	7	3
Survival status		
Alive	143	51
Died of disease	112	40
Died of other causes	23	8

MFH = malignant fibrous histiocytoma; MPNT = malignant peritoneal nerve tumor.

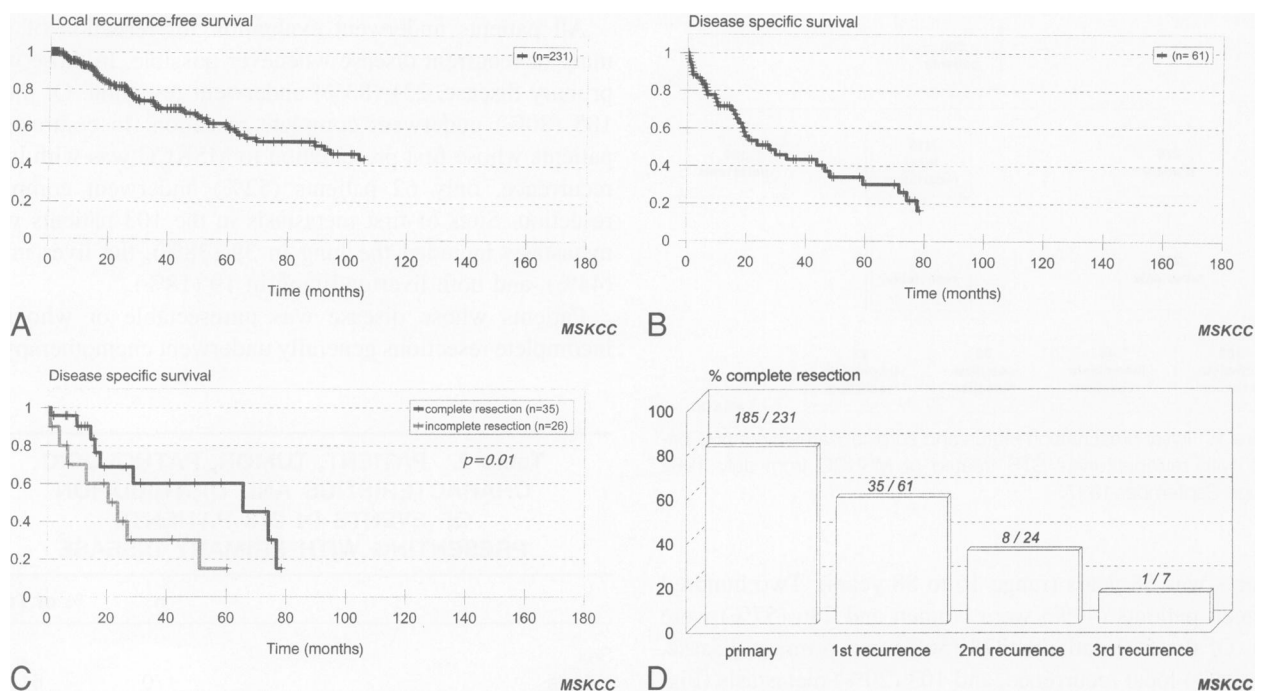


Figure 3. (A) Kaplan–Meier local recurrence-free survival in patients with primary disease who underwent resection. Of the 231 patients with primary disease who then underwent resection, local recurrence subsequently developed in 61. Local recurrence-free survival was 81% (CI 76% to 86%) at 2 years and 59% (CI 55% to 63%) at 5 years. (B) Kaplan–Meier disease-specific survival after local recurrence developed in patients with primary disease. Of the patients with primary disease, 231 underwent complete resection. Of these, local recurrence developed in 61. Median survival after local recurrence was 28 months, the same as those (see Fig. 2) with local recurrence. (C) Kaplan–Meier disease-specific survival after local recurrence developed in patients with primary disease, divided by resection of recurrence. Of the 61 patients in whom local recurrence developed, 35 (57%) underwent complete resection. This was significant for predicting subsequent survival ($p = 0.01$). (D) Rate of complete resection for primary disease and after the first, second, and third local recurrences. The number of patients who underwent complete resection, divided by those undergoing attempted resection, is indicated on the curve. The rate of complete resection was 80%, 57%, 33%, and 14%, respectively.

radiation. A total of 172 patients underwent doxorubicin-based chemotherapy, 95 of these at MSKCC and 77 at outside institutions. A total of 173 patients had adjuvant radiation treatment. Of these, 119 had radiation at MSKCC, which included external beam in 66, brachytherapy in 30, and intraoperative radiation in 23. An additional 54 patients had undergone radiation before presenting for treatment at MSKCC.

To evaluate and compare subset prognosis and the impact of uniform surgical management, survival analyses were next performed on the homogenous group of 278 patients who presented to MSKCC with primary disease. All of these patients underwent treatment at MSKCC based on the same treatment algorithm. All patients were accurately staged and then underwent abdominal exploration using a transperitoneal approach, and resection where appropriate. The distribution of clinical and pathologic characteristics in these 278 patients is illustrated in Table 2. Resection was performed in 231 of these patients (83%). Resectability was not associated with tumor size, grade, or histologic subtype (data not shown). Resection of contiguous organs was performed in 178 patients (77%) and included *en bloc* resection

of retroperitoneal organs, including kidney, adrenal, pancreas, spleen, colon, uterus, bladder, and vascular resection (inferior vena cava, iliac artery, vein) when indicated. Incomplete resection was defined as a resectional operation where gross residual disease was obvious after resection. Of the 231 patients who underwent resection, 185 (80%) were completely resected and 46 had gross residual disease after resection. Of the 185 patients who were completely resected, 136 (74%) had negative microscopic margins. Patients were deemed as having unresectable disease ($n = 47$) if they had distant metastases, peritoneal implants, or extensive vascular involvement. The perioperative (30-day) mortality rate from surgery was 4%, with nine patients who died as a complication of operation. Causes of death included bleeding, sepsis, myocardial infarction, and multi-system organ failure.

With a median follow-up of 28 months, local recurrence developed in 61 patients, distant metastasis developed in 30 patients, and 112 patients died of their disease. This included 21 patients whose disease was unresectable and who died of disease from an unresectable primary tumor without manifesting local or metastatic recurrence.

Table 3. ANALYSIS OF LOCAL RECURRENCE FREE SURVIVAL IN 231 PRIMARY RETROPERITONEAL SARCOMA PATIENTS WITH RESECTABLE DISEASE

	n	p value* (Univariate)	p value (Multivariate)	Relative Risk† (CI)
Sex		0.06		
Male	140			
Female	91			
Age		0.9		
>50 years	156			
<50 years	75			
Grade		0.05		
High	134		0.01	2.0 (1.2–3.4)
Low	97			
Size		0.07		
>10 cm	170			
≤10 cm	59			
Histologic subtype		0.02		
Liposarcoma	109		0.01	2.6 (1.5–4.6)
Others	58			
Leiomyosarcoma	48			
Fibrosarcoma	16			
Surgical resection margins		0.2		
Negative micro & gross margins	136			
Positive micro & negative gross margins	49			
Positive micro & gross margins	46			

* Univariate p refers to log rank test of no difference vs any difference between categories.

† Relative risk to other categories of the same factor.

CI = confidence interval.

Analysis of Disease-Free Survival

Local Recurrence-Free Survival

The analysis of local recurrence-free survival was confined to the 231 patients who presented to MSKCC with primary disease and then underwent resection (Fig. 3A). Local recurrence-free survival was 81% (CI 76% to 86%) at 2 years and 59% (CI 55% to 63%) at 5 years (Table 3). Factors predictive for local recurrence included high histologic grade ($p = 0.01$, RR = 2) and liposarcoma histologic subtype ($p = 0.01$, RR = 2.6).

Disease-specific survival after the first local recurrence is depicted in Figure 3B. Median survival after local recurrence was 28 months, similar to that of patients presenting to MSKCC with local recurrence. Of the 61 patients in whom a first local recurrence developed, 35 (57%) underwent complete resection. In the remaining 26 patients, there was residual gross disease after resection or their disease was unresectable. Complete resection was a significant variable predicting survival after local recurrence (see Fig. 3C). The resection rate decreased after each subsequent local recurrence; thus, after the second local recurrence the resection rate was 22%, and after the third local recurrence it was 10% (see Fig. 3D).

Metastasis-Free Survival

The analysis of metastasis-free survival was confined to the 231 patients who presented to MSKCC with primary

disease and then underwent resection (Fig. 4A). Metastasis-free survival was 88% (CI 86% to 90%) at 2 years and 79% (CI 76% to 82%) at 5 years. Sites of metastasis included lung in 14 patients, liver in 10 patients, and lung and liver in 4 patients (Table 4). Factors predictive for metastasis include high histologic grade ($p = 0.01$, RR = 5) and positive gross and microscopic margins of resection ($p = 0.01$, RR = 3.9). Postmetastasis survival is shown in Figure 4B. Median survival after metastasis was 13 months, similar to that in patients presenting to MSKCC with metastasis.

Analysis of Disease-Specific Survival

During the time of follow-up, 112 patients died of disease and 23 patients died of other causes. The median survival was 72 months and the 5-year actuarial survival was 54% (CI 50% to 58%). On both univariate and multivariate analysis (Table 5), unresectable disease ($p = 0.001$, RR = 4.7), incomplete resection ($p = 0.001$, RR = 4), and high histologic grade ($p = 0.001$, RR = 3.2) were predictive of disease-specific death. Figure 5 depicts Kaplan–Meier disease-specific survival divided by surgical resection. Of the 231 patients whose disease was resectable, 185 underwent complete resection with gross negative margins. The median survival of this group was 103 months. In contrast, the median survival in patients ($n = 46$) undergoing incomplete resection was 18 months. There was no significant difference in survival between patients whose disease was unre-

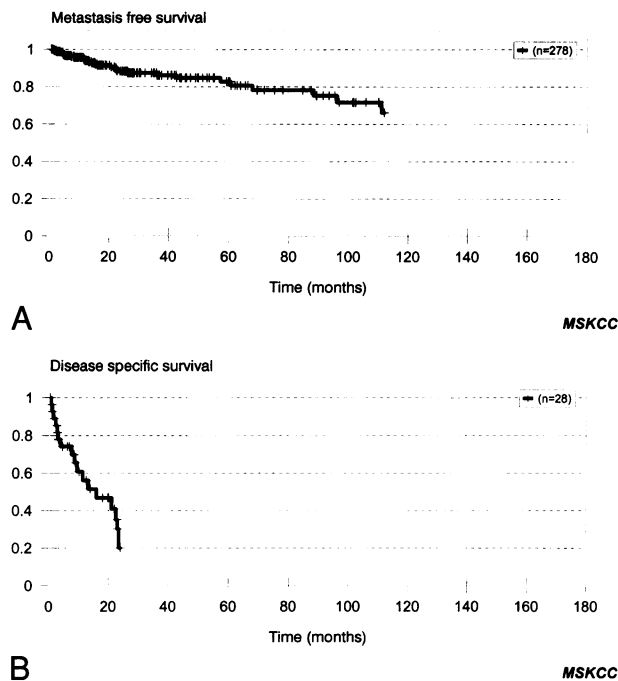


Figure 4. (A) Kaplan-Meier local metastasis-free survival in patients with primary disease who underwent resection. Of the 231 patients with primary disease who then underwent resection, metastasis subsequently developed in 28. Metastasis-free survival was 88% (CI 86% to 90%) at 2 years and 79% (CI 76% to 82%) at 5 years. (B) Kaplan-Meier disease-specific survival after the development of metastasis in patients with primary disease. Median survival after local recurrence was 13 months, similar to that in patients (see Fig. 2) with metastasis.

sectable and those who underwent incomplete resection ($p = 0.4$).

The effect of high histologic grade on survival is illustrated in Figure 6. The median survival of patients with high-grade tumors was 33 months in contrast to 149 months for those with low-grade tumors. Conversely, the size of the primary tumor did not appear to affect survival. However, the survival of patients with tumors >10 cm was consistently lower, and the two deaths in patients with tumors 5 to 10 cm at 110 and 140 months obscures this relation.

To balance the variables in patients who underwent complete resection, we performed a further multivariate analysis on the subset of patients ($n = 231$) who had resectable disease. Table 6 summarizes both univariate and multivariate analyses of these patients. In this selected group of patients, in addition to high grade and incomplete resection, size >10 cm ($p = 0.04$, RR = 2) and positive microscopic margins ($p = 0.03$, RR = 1.9) predicted death from disease.

DISCUSSION

The first report with regard to retroperitoneal STS from MSKCC emphasized the need for aggressive surgical management.⁸ Nearly half a century later, similar principles apply. In the current study, presentation status, unresectable primary tumor, positive gross margins, and high histologic

grade are strongly associated with the tumor mortality rate. These variables are in part a function of tumor biology and in part a function of the ability to deliver adequate treatment.

We report our experience with 500 patients who had either primary or recurrent disease. Not surprisingly, presentation status strongly influenced outcome. Thus, patients with primary disease have a median survival of 72 months *versus* 28 months for those with local recurrence and 10 months for those with metastasis. When we followed the patients who presented to us with primary disease to the time of local or metastatic recurrence, the postrecurrence survival time was similar to the stage-matched survival of all 500 patients. This suggests that earlier diagnosis and treatment may represent lead-time bias, and that survival is very much a function of tumor biology. This begs two questions: does treatment have an impact on survival, or is the ability to deliver treatment associated with and defined by tumor biology? Given that only complete resection translates into survival benefit, the first surgical procedure may well determine outcome. Conversely, after the first recurrence, tumor biology determines outcome.

When we analyzed the patients who presented to us with primary disease, we found a resection rate of 83%. This represents an aggressive approach to resection by a group of specialized and experienced surgeons. Several authors have reported similar rates;⁹⁻¹¹ others report lower rates.^{12,13} These data are summarized in Table 6. As important as resection is the ability to resect the tumor completely with gross negative margins. The median survival of patients who underwent complete resection was 103 months. This is predicated on a liberal *en bloc* resection policy to obtain negative margins even when contiguous organs are not directly invaded but approximate the margin of resection.¹⁴ Conversely, the median survival of patients undergoing incomplete resection was 18 months; this was no different from performing no resection at all. Partial resection should therefore be reserved for patients who have significant symptoms that can be palliated by surgery.

One series has reported a resection rate of 95% and survival that is similar to that for extremity tumors.⁹ Part of the explanation for these reported differences is that in this study⁹ it appears that the resection rate was based on patients referred for surgery. In contrast, our denominator includes all patients referred for evaluation and treatment. The lower rate we report may also reflect the nature of the tertiary referral pattern to MSKCC. It is nonetheless our experience that anatomic site is indeed an important prognostic factor in STS, and the prognosis for retroperitoneal tumors is considerably worse than for extremity tumors.¹ This observation is at least in part dependent on the recognition that, in marked contrast to extremity STS, patients with retroperitoneal sarcoma can and do die from local recurrence.¹⁵

These differences may reflect diverse biology and the impact of anatomic location on the ability to apply local

Table 4. ANALYSIS OF DISTANT METASTASIS FREE SURVIVAL IN 231 PRIMARY RETROPERITONEAL SARCOMA PATIENTS WITH RESECTABLE DISEASE

	n	p value* (Univariate)	p value (Multivariate)	Relative Risk† (CI)
Sex		0.8		
Male	140			
Female	91			
Age		0.8		
>50 years	156			
<50 years	75			
Grade		0.01	0.01	5.0 (1.7–15)
High	134			
Low	97			
Size		0.6		
>10 cm	170			
≤10 cm	59			
Histological subtype		0.01		
Liposarcoma	109		0.01	0.2 (0.07–0.7)
Others	58			
Leiomyosarcoma	48			
Fibrosarcoma	16			
Surgical resection margins		0.01		
Negative micro & gross margins	136			
Positive micro & negative gross margins	49			
Positive micro & gross margins	46		0.01	3.9 (1.6–9.5)

* Univariate p refers to log rank test of no difference vs any difference between categories.

† Relative risk to other categories of the same factor.

CI = confidence intervals.

treatment. A good correlate of this is the capability of adjuvant radiation therapy to reduce local recurrence. In extremity STS, all investigations examining adjuvant radiation therapy have demonstrated improved local control over surgery alone.^{16–21} This has been far more difficult to validate for retroperitoneal sarcoma, at least to some extent because of the difficulty in delivering adequate radiation to the retroperitoneum without toxicity.^{13,22–26} The most common histologic subtype, liposarcoma, is associated with local recurrence and negatively associated with metastasis. This reconfirms the principle that most patients with retroperitoneal disease die of local recurrence.

There are several other differences between extremity and retroperitoneal tumors. Death from extremity tumors, although associated with local recurrence, is almost always consequent on metastasis.²⁷ In contrast, most patients who die of retroperitoneal sarcoma die of local recurrence. Thus, of the patients who had primary disease, 84 of 112 (75%) died in the absence of metastasis. This difference is probably a function of anatomic location and possibly tumor biology.

Most authors report high local recurrence rates for retroperitoneal sarcoma, ranging from 40% to 80%.^{2,10,28–31} When we separated patients with primary disease, the median time to local recurrence was greater than 5 years. This is a longer median time than previously

reported² and probably reflects our current analysis of a homogenous group of patients with primary disease. Although we did not address the role of follow-up in the resected patient, our policy has been to follow asymptomatic patients with clinical evaluation every 3 months and obtain abdominal computed tomography scans every 6 to 12 months for the first 3 years. With increasing experience, we have become less aggressive about trying to use imaging studies to determine asymptomatic recurrence, especially after the second recurrence. Discussions about trials of varying follow-up strategies have been complicated by the reluctance of physicians and patients to be compliant both for or against intense follow-up. It is thus unclear whether earlier detection of recurrence by imaging facilitates resection or adds lead-time bias to postrecurrence survival.

In the patient with a first local recurrence and no metastases, we frequently perform reexploration. The rationale for liberal reexploration in patients with a first recurrence is predicated on the finding that median survival after local recurrence is 60 months in resected patients *versus* 20 months in unresected patients. Recurrent tumors were resected in 57% of patients with a first recurrence. This figure declines precipitously with further recurrences, falling to 20% after the second recurrence and 10% after the third. This probably reflects increasingly aggressive disease and

Table 5. ANALYSIS OF DISEASE SPECIFIC SURVIVAL IN 278 PRIMARY RETROPERITONEAL SARCOMA PATIENTS

	n	p value* (Univariate)	p value (Multivariate)	Relative Risk† (CI)
Sex		0.6		
Male	170			
Female	108			
Age		0.08		
>50 years	183			
<50 years	95			
Grade		0.001	0.001	3.2 (2.0–5.0)
High	168			
Low	110			
Size		0.2	0.02	1.7 (1.1–2.7)
>10 cm	196			
≤10 cm	80			
Histological subtype		0.08		
Liposarcoma	116			
Others	87			
Leiomyosarcoma	63			
Fibrosarcoma	22			
Surgical resection margins		0.001		
Negative micro & gross margins	136			
Positive micro & negative gross margins	49			
Unresectable	47		0.001	4.7 (2.9–7.5)
Positive micro & gross margins	46		0.001	4.0 (2.5–6.5)

* Univariate p refers to log rank test of no difference vs any difference between categories.

† Relative risk to other categories of the same factor.

CI = confidence intervals.

the technical difficulty associated with multiple abdominal operations.

The value of chemotherapy and radiation therapy is difficult to evaluate. Given that most recurrences are local, local adjuvant therapy such as intraperitoneal chemotherapy or experimental immunotherapy is attractive, in theory.³² Unfortunately, our efforts have not as yet provided an adequate or evaluable approach.

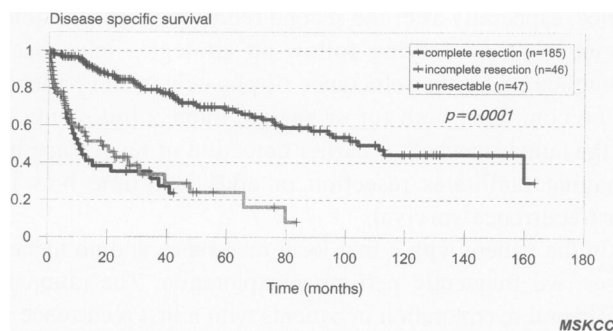


Figure 5. Kaplan–Meier disease-specific survival divided by surgical resection. Of the 231 patients whose disease was resectable, 185 underwent complete resection with gross negative margins. The median survival of this group was 103 months. In contrast, the median survival in those (n = 46) undergoing incomplete resection was 18 months. There was no significant difference in survival between patients whose disease was unresectable and those who underwent incomplete resection (p = 0.4).

CONCLUSIONS

In this study of patients with retroperitoneal sarcoma, presentation status, high histologic grade, unresectable primary tumor, and positive gross margins are strongly associated with death from tumor. Patients with primary disease or a first local recurrence approached with curative intent should undergo aggressive attempts at complete surgical resection. This should include a liberal *en bloc* resection policy to obtain negative margins. Incomplete resection should be undertaken only for symptom relief.

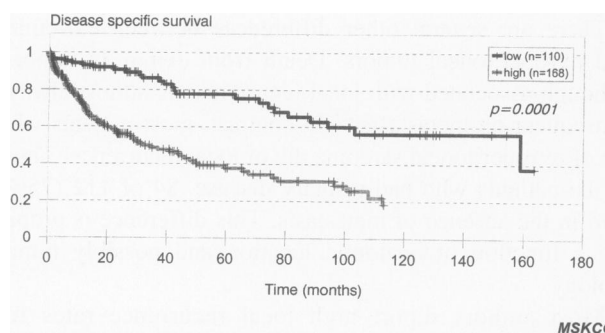


Figure 6. Kaplan–Meier disease-specific survival divided by tumor grade. The median survival of patients with high-grade tumors was 33 months versus 149 months for those with low-grade tumors. Tumor grade did not affect the resectability of the tumor.

Table 6. COMPARISON OF COMPLETE RESECTION AND SURVIVAL FOR RETROPERITONEAL SOFT TISSUE SARCOMA

Series	Years Studied	n	Complete Resection (%)	5-year Survival (%)
Cody (MSKCC) ²⁹	1951–1974	47	50	40
Kinsella (NCI) ¹³	1980–1985	35	60	40
Jaques (MSKCC) ²	1982–1987	114	69	74
Karakousis (SUNY) ⁹	1990–1995	88	95	66
Kilkenny ³⁰ (Gainesville)	1970–1994	63	78	56
Current (MSKCC)	1982–1997	500	80	70

Acknowledgments

The authors thank Nicole Maurice and Gina DiMartino for their excellent data management. They also gratefully acknowledge our colleagues on the Gastric & Mixed Tumor Service, Department of Surgery, the Gastrointestinal Oncology Service, Department of Medicine and Department of Radiation Oncology, who have helped care for these patients.

References

- Lewis JJ, Brennan MF. Soft tissue sarcomas. *Curr Probl Surg* 1996; 33:817–872.
- Jaques DP, Coit DG, Hajdu SI, Brennan MF. Management of primary and recurrent soft-tissue sarcoma of the retroperitoneum. *Ann Surg* 1990; 212:51–59.
- Karakousis CP, Gerstenbluth R, Kontzoglou K, Driscoll DL. Retroperitoneal sarcomas and their management. *Arch Surg* 1995; 130:1104–1109.
- Lewis JJ, Benedetti F. Adjuvant therapy for soft tissue sarcomas. *Surg Oncol Clin North Am* 1997; 6:847–862.
- Hajdu SI, Shiu MH, Brennan MF. The role of the pathologist in the management of soft tissue sarcomas. *World J Surg* 1988; 12:326–331.
- Gaynor JJ, Tan CC, Casper ES, et al. Refinement of clinicopathologic staging for localized soft tissue sarcoma of the extremity: a study of 423 adults. *J Clin Oncol* 1992; 10:1317–1329.
- Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Statist Assoc* 1958; 53:457–462.
- Pack GT, Tabah EJ. Primary retroperitoneal tumors: a study of 120 cases. *Surg Gynecol Obstet* 1954; 99:209–231.
- Karakousis CP, Kontzoglou K, Driscoll DL. Resectability of retroperitoneal sarcomas: a matter of surgical technique? *Eur J Surg Oncol* 1995; 21:617–622.
- Singer S, Corson JM, Demetri GD, Healey EA, Marcus K, Eberlein TJ. Prognostic factors predictive of survival for truncal and retroperitoneal soft-tissue sarcoma. *Ann Surg* 1995; 221:185–195.
- Storm FK, Eilber FR, Mirra J, Morton DL. Retroperitoneal sarcomas: a reappraisal of treatment. *J Surg Oncol* 1981; 17:1–7.
- Storm FK, Mahvi DM. Diagnosis and management of retroperitoneal soft-tissue sarcoma. *Ann Surg* 1991; 214:2–10.
- Kinsella TJ, Sindelar WF, Lack E, et al. Preliminary results of a randomized study of adjuvant radiation therapy in resectable adult retroperitoneal soft tissue sarcomas. *J Clin Oncol* 1988; 6:18–25.
- Russo P, Kim Y, Ravindran S, Huang W, Brennan MF. Nephrectomy during operative management of retroperitoneal sarcoma. *Ann Surg Oncol* 1997; 4:421–424.
- Lewis JJ, Brennan MF. Soft tissue sarcomas. In Sabiston, ed. *The biological basis of modern surgical practice*. New York: WB Saunders, 1997:528–534.
- Lindberg RD, Martin RG, Romsdahl MM, Barkley HT Jr. Conservation surgery and postoperative radiotherapy in 300 adults with soft-tissue sarcomas. *Cancer* 1981; 47:2391–2397.
- Potter DA, Glenn J, Kinsella T, Glatstein E. Patterns of recurrence in patients with high-grade soft-tissue sarcomas. *J Clin Oncol* 1985; 3:353–366.
- Leibel SA, Tranbaugh RF, Wara WM, et al. Soft tissue sarcomas of the extremities: survival and patterns of failure with conservative surgery and postoperative irradiation compared to surgery alone. *Cancer* 1982; 50:1076–1083.
- Suit HD, Mankin HJ, Wood W, Proppe KH. Preoperative, intraoperative and postoperative radiation in the treatment of primary soft tissue sarcoma. *Cancer* 1985; 55:2659–2667.
- Brennan MF, Hilaris B, Shiu MH, et al. Local recurrence in adult soft tissue sarcoma. A randomized trial of brachytherapy. *Arch Surg* 1987; 122:1289–1293.
- Harrison LB, Franzese F, Gaynor JJ, Brennan MF. Long-term results of a prospective trial of adjuvant brachytherapy in the management of completely resected soft tissue sarcomas of the extremity and superficial trunk. *Int J Radiat Oncol Biol Phys* 1993; 27:259.
- Rosenberg SA, Kent H, Costa J, et al. Prospective randomized evaluation of the role of limb-sparing surgery, radiation therapy, and adjuvant chemioimmunotherapy in the treatment of adult soft-tissue sarcomas. *Surgery* 1978; 84:62–69.
- Clark JA, Tepper JE. Role of radiation therapy in retroperitoneal sarcomas. *Oncology* 1996; 10:1867–1872.
- Ueda T, Aozasa K, Tsujimoto M, et al. Multivariate analysis for clinical prognostic factors in 163 patients. *Cancer* 1988; 62:1444–1450.
- Tepper JE, Suit HD, Wood WC, et al. Radiation therapy of retroperitoneal soft tissue sarcomas. *Int J Radiat Oncol Biol Phys* 1984; 10:825–830.
- Willett CG, Suit HD, Tepper JE, et al. Intraoperative electron beam radiation therapy for retroperitoneal soft tissue sarcoma. *Cancer* 1991; 68:278–283.
- Lewis JJ, Leung D, Heslin M, Woodruff JM, Brennan MF. Association of local recurrence with subsequent survival in extremity soft tissue sarcoma. *J Clin Oncol* 1997; 15:646–652.
- Alvarenga JC, Ball AB, Fisher C, et al. Limitations of surgery in the treatment of retroperitoneal sarcoma. *Br J Surg* 1991; 78:912–916.
- Cody HS, Turnbull AD, Fortner JG, Hajdu SI. The continuing challenge of retroperitoneal sarcomas. *Cancer* 1981; 47:2147–2152.
- Kilkenny JW, Bland KI, Copeland EM. Retroperitoneal sarcoma: the University of Florida experience. *J Am Coll Surg* 1996; 182:329–339.
- McGrath PC, Neifeld JP, Lawrence W, Jr., et al. Improved survival following complete excision of retroperitoneal sarcomas. *Ann Surg* 1984; 200:200–204.
- Lewis JJ, Houghton AN. Definition of tumor antigens suitable for vaccine construction. *Semin Cancer Biol* 1995; 6:321–327.

Discussion

DR. WALTER LAWRENCE, JR. (Richmond, Virginia): For those of you who don't focus on soft tissue sarcomas, you must realize that