Histologic Subtype and Margin of Resection Predict Pattern of Recurrence and Survival for Retroperitoneal Liposarcoma

Samuel Singer, MD, Cristina R. Antonescu, MD,† Elyn Riedel, MA,‡ and Murray F. Brennan, MD**

Objective: The aim of this study was to determine the pattern of recurrence and prognostic significance of histologic subtype in a large series of patients with primary retroperitoneal liposarcoma.

Summary Background Data: Classification of liposarcoma into subtypes, based on morphologic features and cytogenetic aberrations, is now widely accepted. Previous studies have shown that high histologic grade and incomplete gross resection are the most important prognostic factors for survival in patients with retroperitoneal sarcoma and suggest that patients with liposarcoma have a 3-fold higher risk of local recurrence compared with other histologies.

Methods: A prospective database was used to identify 177 patients with primary retroperitoneal liposarcoma treated between July 1982 and June 2002. Histology at primary presentation was reviewed by a sarcoma pathologist and subtyped into 4 distinct groups according to strict criteria. The influence of clinicopathological factors on local recurrence, distant recurrence, and disease-specific survival was analyzed.

Results: Of 177 patients with primary retroperitoneal liposarcoma operated on for curative intent, 99 (56%) presented with well-differentiated, 65 (37%) with dedifferentiated, 9 (5%) with myxoid, and 4 (2%) with round cell morphology. The tumor burden was determined by the sum of the maximum tumor diameters. The median tumor burden was 26 cm (5–139). Median follow-up time for 92 (52%) surviving patients was 37 (mean, 0.5–192) months. Multivariate analysis showed that dedifferentiated liposarcoma subtype was associated with a 6-fold increased risk of death compared with well-differentiated histology ($P < 0.0001$). In addition to histologic subtype, incomplete resection ($P < 0.0001$), contiguous organ resection (excluding nephrectomy; $P = 0.05$), and age ($P = 0.03$) were important independent prognostic factors for survival in retroperitoneal liposarcoma. Retroperitoneal dedifferentiated liposarcoma was associated with an 83% local recurrence rate and 30% distant recurrence rate at 3 years.

Conclusions: The histologic subtype and margin of resection are prognostic for survival in primary retroperitoneal liposarcoma. Dedifferentiated histologic subtype and the need for contiguous organ resection (excluding nephrectomy) was associated with an increase risk of local and distant recurrence. Nephrectomy may be needed to achieve complete resection, but has no measurable influence on disease specific survival.

(*Ann Surg* 2003;238: 358–371)

Liposarcoma (LS) is the single most common soft tissue sarcoma and accounts for at least 20% of all sarcomas in adults.[1] Classification of LS into 4 types, based on morphologic features and cytogenetic aberrations, is now widely accepted.[2] These 4 types are (1) well-differentiated; (2) dedifferentiated; (3) myxoid/round cell; and (4) pleomorphic. The extent of differentiation, as reflected by histologic grade, remains the most important determinant of clinical course and of ultimate prognosis for patients with LS after resection. The anatomic distribution of LS appears to be closely related to histologic type: myxoid/round cell and pleomorphic LS have a predilection for the extremities, whereas well-differentiated/dedifferentiated LS occurs predominantly in the retroperitoneum. Well-differentiated LS often recur locally but have minimal metastatic potential, with a 5-year survival probability of 90%. Deaths result from local effects on critical adjacent organs, usually in the retroperitoneum.[3–6] Dedifferentiated lesions have similar local effects. Although they metastasize systemically (eg, to lungs), they have a significantly lower metastatic rate (10–15%) than would be predicted given their high-grade morphology, and a 5-year survival probability of 75%.[7] The myxoid/round cell LS represents a morphologic continuum, and histologic grading is based on the extent of round cell component. Recent work from our group at Memorial Sloan-Kettering Cancer Center (MSKCC) found that patients with low-grade myxoid LS, defined as <5% round cell areas, have a 5-year survival of 90%, whereas those patients with high-grade myxoid/round cell LS (>5% round cells) has a 5-year survival probability of 60%.[8] Pleomorphic LS, the least common subtype, are high-grade, very aggressive tumors with a high metastatic potential and a 5-year survival probability of 30–50%.[9]

Presented at the American Surgical Association Annual Meeting, Washington, DC, April 24–26, 2003.

From the *Sarcoma Disease Management Team, Department of Surgery, †Department of Pathology, and ‡Department of Epidemiology and Biostatistics, Memorial Sloan-Kettering Cancer Center, New York, NY.

Reprints: Samuel Singer, MD, Sarcoma Disease Management Team, Department of Surgery, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, NY. 10021. E-mail: singers@mskcc.org.

0003-4932/03/23803-0358

DOI: 10.1097/01.sla.0000086542.11899.38

The treatment of retroperitoneal LS continues to be a challenge for the surgeon, given their large size and often central location. The ability to completely resect a retroperitoneal sarcoma remains the most important predictor of local recurrence and overall survival.[4,5,10] Most retroperitoneal LS are large (>10 cm) at the time of diagnosis and because of the high degree of adipocyte differentiation, are difficult to distinguish from normal retroperitoneal fat. Thus, it is often difficult to obtain a margin of normal tissue around the tumor. The large size and extent of these tumors make treatment with tumoricidal doses of adjuvant radiation difficult and are often associated with substantial morbidity. For the low-grade, well-differentiated LS, adjuvant chemotherapy has little to offer, given the very low mitotic rate of these lesions. The use of adriamycin and ifosfamide chemotherapy for the higher grade subtypes, such as dedifferentiated, myxoid/round cell, or pleomorphic LS results in partial responses in up to 50% of patients[11] without a demonstrable improvement in overall survival. Furthermore, complete response rates to chemotherapy have been seen in less than 10% of patients. Thus, complete surgical resection continues to be the most important component of therapy. The present study was undertaken to determine the influence of histologic subtype and extent of surgical resection on patterns of recurrence and overall survival in a large series of patients with primary retroperitoneal LS.

METHODS

All patients treated for soft-tissue sarcoma at Memorial Sloan-Kettering Cancer Center between July 1, 1982, and December 31, 2001, were entered in a prospectively maintained database. For the present study, all patients with primary retroperitoneal LS and malignant fibrous histiocytoma were considered for histologic review. In the present study primary retroperitoneal LS was classified into 4 histologic types based on recent World Health Organization criteria as (1) well-differentiated, (2) dedifferentiated, (3) myxoid/round cell, and (4) pleomorphic. After histologic reclassification, there were 177 patients with confirmed primary retroperitoneal LS that had surgical resection at MSKCC and had complete clinicopathologic data for correlation to clinical outcome. None of the patients had distant metastasis at the time of presentation. Standard evaluation of patients included a history and physical examination, complete blood count, and serum chemistry analyses. Computed tomography scans of the chest, abdomen, and pelvis were also obtained. Patient, tumor, treatment, and survival data were prospectively acquired and entered into our sarcoma database. Approval was obtained from the MSKCC IRB for this study.

Patient demographics included age at diagnosis and sex. Tumor burden was determined by the sum of the maximum diameter of the primary tumors as reported at the time of initial surgical resection. The type of surgery performed (total or subtotal resection) as well as adjacent organs removed was ascertained from the operating surgeons assessment as documented on the operative report. Specimen margins were analyzed for evidence of microscopic disease. Fourteen (8%) of the patients received postoperative external beam radiation therapy. None of the patients received chemotherapy. Patients were observed in our soft tissue sarcoma program at 4-month intervals during the first 2 years and at 6-month intervals thereafter. Information obtained during follow-up included status of disease (alive without disease, alive with recurrent disease, dead of other causes without evidence of recurrent disease, dead of other causes with disease or dead as a result of sarcoma treatment or with sarcoma) and local and distant disease recurrence.

Pathology

The histologic features were reviewed by 1 of the authors (C.A.) and a minimum of 1 hematoxylin and eosin-stained histologic section 4 μm in thickness was examined per centimeter of tumor diameter. Histologic subtype and grade was assigned by following the published criteria of the World Health Organization Classification of Tumors of Soft Tissue and Bone.[12] Histologic subtype was classified as well-differentiated, dedifferentiated, myxoid/round cell, or pleomorphic. Retroperitoneal fatty tumors containing mature adipocytes with occasional atypical cells with irregular hyperchromatic nuclei and rare or absent lipoblasts or those lesions with lipoblasts and minimal fibrosis (<25% of the sampled tumor) were labeled lipoma-like well-differentiated LS. Tumors with atypical stromal cells associated with significant fibrosis (≥25%) were designated as sclerosing well-differentiated LS. Lesions with regions of nonlipogenic spindle cell sarcoma arising within a fatty tumor or in the bed of a previously resected low-grade lipomatous tumor were identified as dedifferentiated LS. The majority of retroperitoneal tumors initially identified as malignant fibrous histiocytoma in the prospective database on careful review for evidence of adjacent areas of well-differentiated LS could be reclassified as dedifferentiated LS. Tumors with uniform round to oval-shaped primitive nonlipogenic mesenchymal cells and a variable number of small or signet-ring lipoblasts in a prominent myxoid stroma with or without delicate arborizing vasculature were classified as myxoid LS. A subset of myxoid LS shows histologic progression to round cell morphology that is characterized by solid sheets of back-to-back primitive round cells with a high nuclear/cytoplasmic ratio and conspicuous nucleoli with no intervening myxoid stroma. Pure myxoid LS are considered low grade. For the present study, high histologic grade was defined as greater than 5% round cell areas. Pleomorphic LS are characterized by pleomorphic spindle and giant cells as well as sheets of pleomorphic lipoblasts,

TABLE 1. Clinicopathologic and Treatment Characteristics in 177 Patients With Primary Retroperitoneal Liposarcoma

Patient Characteristics	N	% of Total
Age, years median (range)	63 (24–89)	
Sex		
Female	69	39
Male	108	61
Variant		
Well differentiated	99	56
Dedifferentiated	65	37
Myxoid	9	5
Round cell	4	2
Grade		
High	69	39
Low	108	61
Tumor burden, cm median (range)	26 (2.3–139)	
Margins		
Negative margins	77	44
Positive micro margins	66	37
Positive gross margins	33	19
Nephrectomy		
No	109	62
Yes	68	38
Contiguous organ resection		
No	130	74
Yes	47	26
Sclerosing tumor (well-differentiated tumors only)		
No	51	51.5
Yes	48	48.5
Radiation for primary disease		
No	163	92
Yes	14	8
Chemotherapy for primary disease		
None	177	100

which contain enlarged and hyperchromatic nuclei scalloped by cytoplasmic vacuoles.

Statistical Methods

The primary end points of the analysis were disease-specific survival (DSS, defined as time from date of surgery to date of death as a result of disease or complication), time to local recurrence (defined as time from date of surgery to date of first local recurrence for patients with complete resections only), and time to distant recurrence (defined as time from date of surgery to date of first distant recurrence). The end points were assessed with respect to the following clinicopathologic and treatment-related variables: age (both as a continuous variable and divided at the median), gender, tumor burden (both as a continuous variable and divided into quartiles), histologic subtype, grade, margins (negative, microscopically positive, grossly positive), nephrectomy performed, extent of contiguous organ resection (whether any of the following resections were performed: pancreas, colon, small bowel, uterus, bladder, spleen, or vascular), and sclerosing subtype (for well-differentiated tumors only). The Log-rank test[13] and Score test[14] were used to check the association of categorical and continuous variables to the primary end points. DSS, time to local recurrence and time to distant recurrence curves were constructed by the Kaplan–Meier product limit method.[15] Three-year estimates of DSS, time to local recurrence, and time to distant recurrence and the corresponding 95% confidence intervals are reported. Those variables significant at the 0.25 level univariately were entered into a Cox proportional

hazards model[14] to identify independent predictors of DSS, time to local recurrence, and time to distant recurrence. Hazard ratios and corresponding 95% confidence intervals are reported.

RESULTS

Patient and Tumor Characteristics

There were a total of 177 patients with primary retroperitoneal LS treated by surgical resection at MSKCC. Patient characteristics are listed in Table 1. There were 69 men and 108 women with a median age of 63 years (range, 24–89 years). The histologic subtype was well differentiated for 99 patients (56%), dedifferentiated for 65 patients (37%), myxoid for 9 patients (5%), and round cell for 4 patients (2%). Of the 99 patients with well-differentiated LS, 48 patients (49%) were of the sclerosing subtype. The histologic grade was low grade for 108 patients (61%) and high grade for 69 patients (39%). The median tumor burden was 26 cm (range, 5–139 cm). Local treatment consisted of surgical resection for all patients with a total gross excision defined as complete resection by the operating surgeon accomplished in 143 patients (81%) and a subtotal resection in the other 33 patients (19%). In 68 patients (38%) nephrectomy was performed, and in 47 patients (27%) resection of a contiguous organ (other than kidney) was performed. Margins were evaluated both grossly and microscopically in 6 dimensions (superior, inferior, medial, lateral, anterior, and posterior). Margins were categorized as clear, microscopically positive, or grossly positive. A clear margin indicated that there was no tumor at least 1 mm or more from the edge of the inked specimen; a microscopically positive margin indicated microscopically discernible extension of tumor to within <1 mm of the edge of the inked specimen. Seventy-seven patients (44%) had clear margins, 66 (37%) had microscopically positive margins, and 33 patients (19%) had grossly positive margins.

DSS Analysis

For the whole group, 92 patients (52%) remain alive at last follow-up, and 64 have died of sarcoma. Twenty-one additional patients died of other causes. The median time to sarcoma-specific death was 83 months (95% CI, 74–169). For all 177 patients, the actuarial overall DSS rate was 73% (95% CI, 66–81%) at 3 years and 60% (52–69%) at 5 years (Fig. 1). The median follow-up for all 92 survivors was 37 months (range, 0.5–192). The univariate analysis of prognostic factors of importance to DSS for all 177 patients with primary retroperitoneal LS is shown in Table 2. Histologic subtype was prognostic for DSS ($P < 0.0001$, Fig. 2). The 3-year and 5-year DSS for tumors with well-differentiated histology was 92% (86–98%) and 83% (75–92%), respectively, compared with 39% (24–54%) and 20% (7–33%), respectively, for tumors with dedifferentiated histology; 4 of the 9 patients with myxoid tumors died of disease after 3

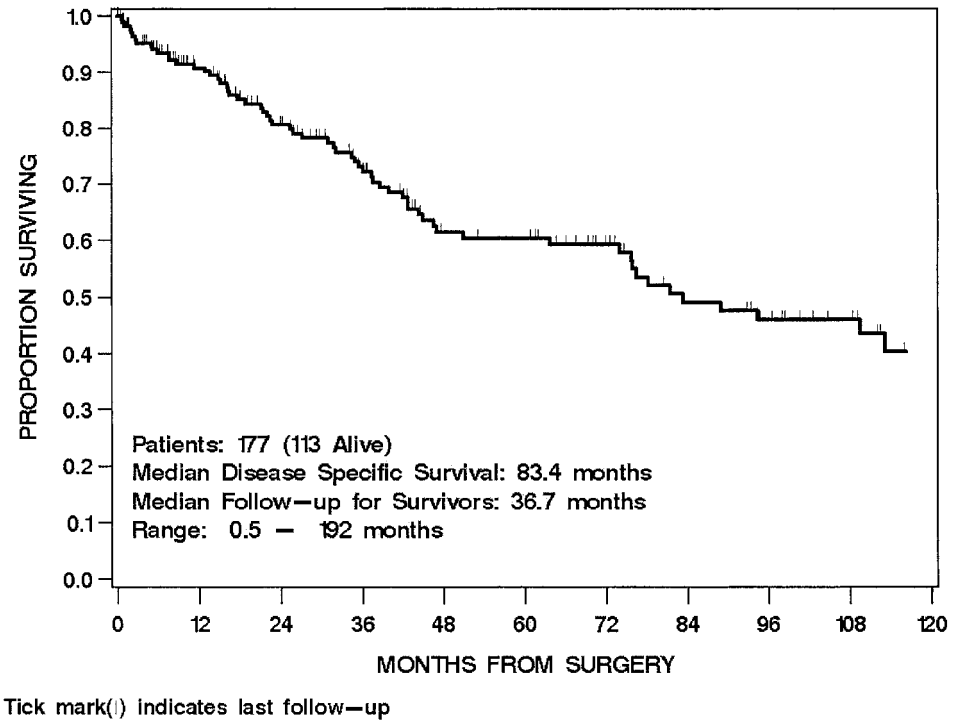

FIGURE 1. DSS for 177 patients with primary retroperitoneal LS.

TABLE 2. Univariate Analysis of Clinicopathologic Variables for Disease-specific Survival in 177 Patients With Primary Retroperitoneal Liposarcoma

	Total	No. of Events	Three-Year Disease-Specific Survival (95% CI)	*P* Value
Overall	177	64	0.73 (0.66–0.81)	
Median survival	83 months		(95% CI, 74–169)	
Variables				
Sex				
Female	69	23	0.73 (0.60–0.85)	0.87
Male	108	41	0.73 (0.64–0.83)	
Age				
Continuous				0.02*
<63	88	26	0.76 (0.66–0.86)	0.02*
≥63	89	38	0.70 (0.59–0.81)	
Variant				
Well differentiated	99	22	0.92 (0.86–0.98)	<0.0001*
Dedifferentiated	65	36	0.39 (0.24–0.54)	
Myxoid	9	4	1	
Round cell	4	2	0.33 (0–0.87)	
Grade				
High	69	38	0.39 (0.24–0.53)	<0.0001
Low	108	26	0.92 (0.87–0.98)	
Tumor burden continuous				0.30
Margins				
Negative margins	77	23	0.87 (0.78–0.95)	<0.0001*
Positive micro margins	66	18	0.70 (0.56–0.84)	
Positive gross margins	33	23	0.43 (0.25–0.62)	
Nephrectomy				
No	109	40	0.73 (0.63–0.82)	0.19*
Yes	68	24	0.74 (0.63–0.86)	
Contiguous organ resection				
No	130	45	0.76 (0.67–0.84)	0.25*
Yes	47	19	0.66 (0.50–0.82)	
Sclerosing tumor (well-differentiated only)				
No	51	11	–	1.0
Yes	48	11	0.92 (0.83–1)	

*Variables included in multivariate model.

years (2 were censored before 3 years) and 2 of the 4 patients with round cell tumors died before 3 years (Fig. 2). DSS according to grade shows the 3-year actuarial DSS rate was 92% (87–98%) for patients with low-grade tumors and 39% (24–53%) for patients with high grade tumors. The difference between these curves is statistically significant ($P < 0.0001$). The association of LS tumor margin status with DSS is shown in Figure 3 and demonstrates improved DSS favoring patients with negative margins after operation ($P < 0.0001$). The 3-year DSS for patients who had operation with negative margins was 87% (78–95%) compared with 70% (56–84%) for patients who had surgery with microscopically positive margins and 43% (25–62%) for patients with gross positive margins. Age, when analyzed as a continuous variable, was prognostic for DSS on univariate analysis ($P = 0.02$). We then categorized age by the median. Age greater than or equal to 63 was associated with a significantly reduced DDS compared with those less than 63 years of age ($P = 0.02$; Fig. 4). For patients greater than or equal to 63 years of age the 3-year DSS was 70% (59–81%) compared with 76% (66–86%) for patients less than 63 years of age. Tumor burden, gender and extent of resection (nephrectomy / contiguous organ resection

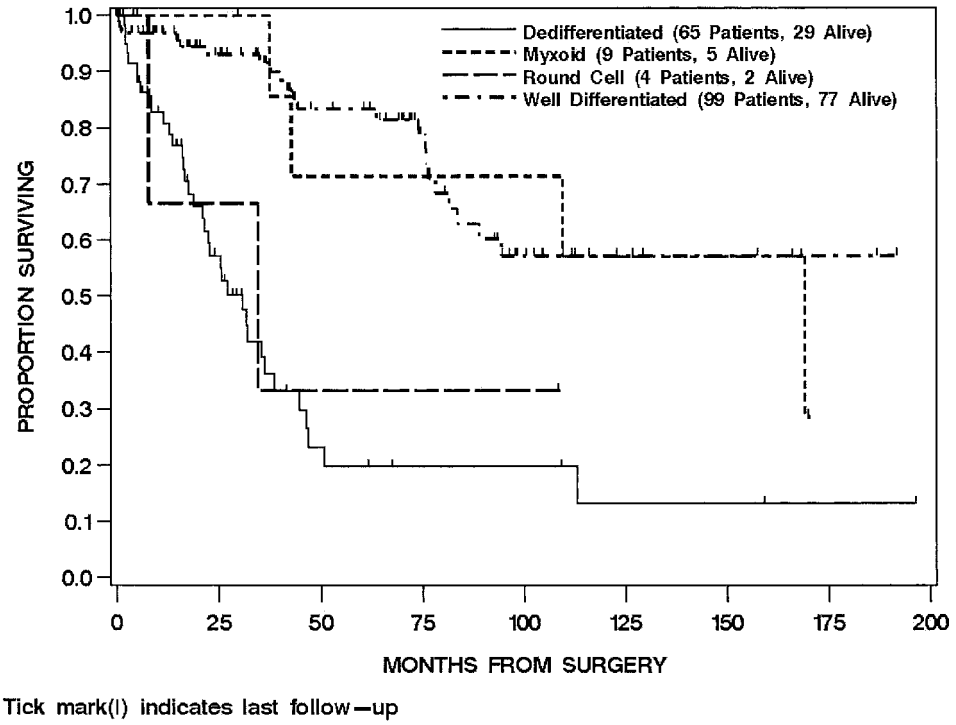

FIGURE 2. DSS by LS histologic subtype.

were not associated with any statistically significant difference in DSS on univariate analysis (Table 2).

Variables significant at the 0.25 level, such as histologic type, margin of resection, nephrectomy, contiguous organ resection (excluding nephrectomy), and age (as a continuous variable), were entered into a multivariate Cox proportional hazards model to identify independent predictors of DSS (Table 3). Given the small number of patients with myxoid and round cell tumors, only patients with well-differentiated and dedifferentiated tumors were included. Because all well-differentiated tumors were low grade and all dedifferentiated tumors were high grade, grade was not included in the multivariate models. The following factors were significantly associated with DSS by Cox regression analysis: dedifferentiated histology versus well differentiated (HR 6, $P < 0.0001$), gross positive margins versus negative margins (HR 4, $P < 0.0001$), contiguous organ resection (excluding nephrectomy) versus no contiguous organ resection (HR 2, $P = 0.05$), and age as a continuous variable (HR 1.03, $P = 0.03$).

Local Recurrence Analysis

For the 144 patients who had complete surgical resections 72 (50%) developed local recurrence at time of last follow-up. The median time to local recurrence was 45 months (95% CI, 30–61). The actuarial probability free of local recurrence was 52% (95% CI, 42–61%) at 3 years and 41% (31–50%) at 5 years. The univariate analysis of prognostic factors of importance to local recurrence for the 144 patients who had complete surgical resection is shown in table 4. Histologic subtype was significantly associated with local recurrence ($P < 0.0001$, see Fig. 5). The probability free of local recurrence at 3 years for well-differentiated, dedifferentiated, and myxoid histologic subtypes was 69% (58–81%), 17% (4–30%), and 57% (20–94%), respectively; the one patient with a round cell tumor who had a complete resection locally recurred. Grade was also associated with time to local recurrence ($P < 0.0001$). High-grade LS had a 3-year probability free of local recurrence of 20% (3–33%) compared with 68% (57–79%) for low-grade LS. The higher probability of local recurrence in patients undergoing contiguous organ resection in contrast to those with no such resection approached statistical significance on univariate analysis ($P = 0.06$). Patients who underwent contiguous organ resection had a 55% (44–66%) 3 year probability free of local recurrence compared with 45% (27–63%) who had no contiguous organs resected. Age, gender, tumor burden, margins, nephrectomy, and sclerosing subtype had no association with local recurrence on univariate analysis (Table 4).

Histologic type and contiguous organ resection were entered into a multivariate Cox proportional hazards model to identify independent predictors of local recurrence (Table 5). Both factors were significantly associated with local recur-

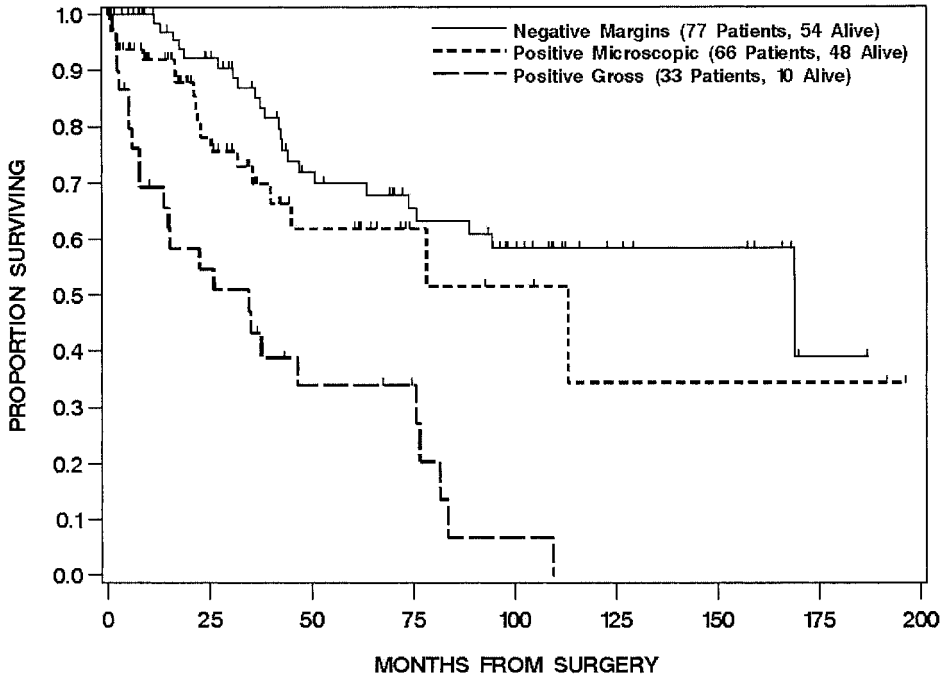

FIGURE 3. DSS by margin status.

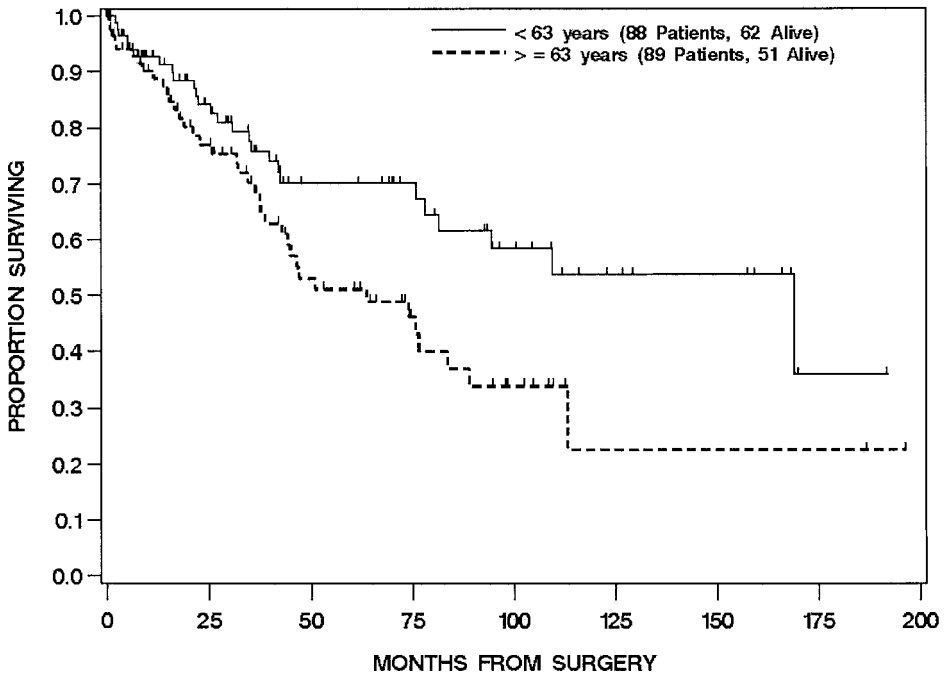

FIGURE 4. DSS by age.

TABLE 3. Predictors of Disease-specific Survival for Retroperitoneal Liposarcoma From Multivariate Analysis (n = 177)

Variable	Hazard Ratio (95% CI)	*P* Value
Age (continuous)	1.03 (1.003–1.05)	0.03
Dedifferentiated vs. well-differentiated	6.0 (3.3–10.9)	<0.0001
Margins		<0.0001 (overall)
Positive microscopic vs. negative	1.1 (0.6–2.2)	0.74
Positive gross vs. negative	3.8 (2.0–7.4)	<0.0001
Contiguous organ resection yes vs. no	1.9 (1.01–3.5)	0.05
Nephrectomy yes vs. no	0.8 (0.5–1.5)	0.50

TABLE 4. Univariate Analysis of Time to Local Recurrence (Patients With Positive Gross Margins are Excluded, n = 144)

	Total	No. of Events	Three-Year Probability free of Local Recurrence (95% CI)	*P* Value
Overall	144	72	0.52 (0.42–0.61)	
Median time to LR	45 months		(95% CI, 30–61)	
Variables				
Sex				
Female	59	26	0.55 (0.39–0.70)	0.73
Male	85	46	0.50 (0.38–0.62)	
Age				
Continuous				0.48
<63	73	35	0.61 (0.48–0.73)	0.36
≥63	71	37	0.43 (0.30–0.57)	
Variant				
Well differentiated	86	33	0.69 (0.58–0.81)	<0.0001*
Dedifferentiated	49	33	0.17 (0.04–0.30)	
Myxoid	8	5	0.57 (0.20–0.94)	
Round cell	1	1	–	
Grade				
High	50	34	0.20 (0.03–0.33)	<0.0001
Low	94	38	0.68 (0.57–0.79)	
Tumor burden continuous				0.74
(0, 16)	35	15	0.43 (0.22–0.64)	0.98
(16,26)	39	19	0.51 (0.33–0.69)	
(26,35)	39	22	0.53 (0.35–0.70)	
>35	31	16	0.59 (0.41–0.78)	
Margins				
Negative margins	77	43	0.55 (0.42–0.68)	0.61
Positive micro margins	66	28	0.50 (0.35–0.64)	
Nephrectomy				
No	81	38	0.52 (0.39–0.65)	0.65
Yes	63	34	0.52 (0.38–0.66)	
Contiguous organ resection				
No	105	50	0.55 (0.44–0.66)	0.06*
Yes	39	22	0.45 (0.27–0.63)	
Sclerosing tumor (well differentiated tumors only)				
No	47	16	0.76 (0.62–0.90)	0.33
Yes	39	17	0.62 (0.44–0.80)	

*Variables included in multivariate model.

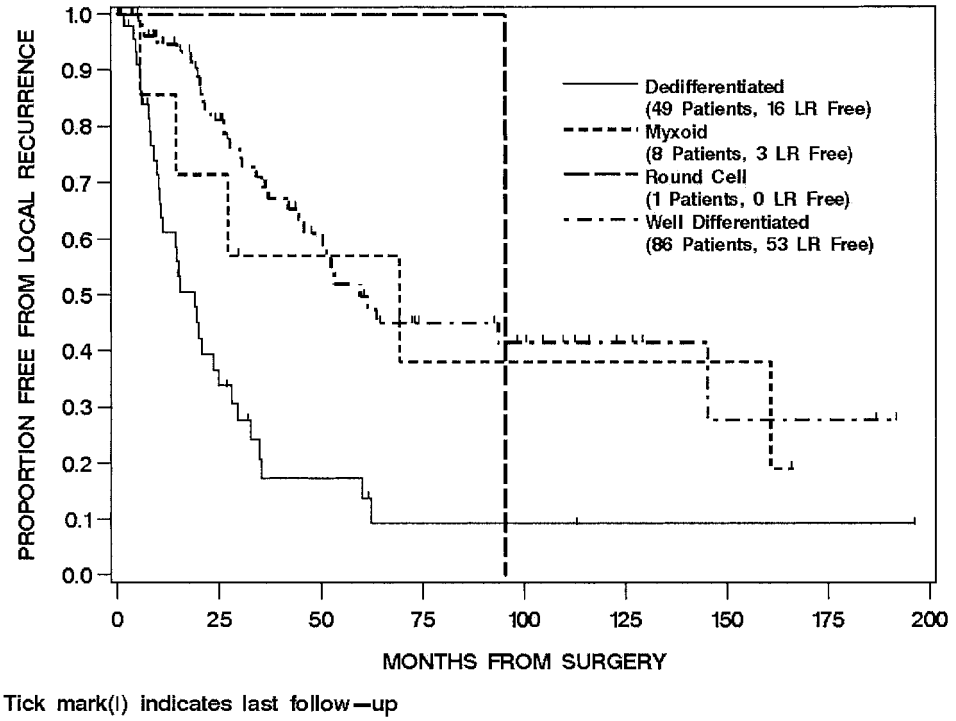

FIGURE 5. Probability free of local recurrence by histologic subtype.

rence by Cox regression analysis: dedifferentiated histology versus well-differentiated (Hazard ratio [HR] 3.6, $P < 0.0001$) and contiguous organ resection versus no contiguous organ resection (HR 1.7, $P = 0.04$).

Distant Recurrence Analysis

For the whole group of 177 patients, 19 (11%) developed distant recurrence at time of last follow-up. Of the 19 patients who developed distant recurrences, 15 were to lung, 5 to liver, and 1 to soft tissue (with some patients having more than 1 site of distant recurrence). The median time to distant recurrence was not reached. For all 177 patients, the actuarial probability free of distant recurrence was 89% (95% CI, 84–94%) at 3 years. The important prognostic factors for distant recurrence on univariate analysis are shown in Table 6. Histologic subtype was significantly associated with distant recurrence on univariate analysis ($P < 0.000$; Fig. 6). The probability free of distant recurrence at 3 years for well-differentiated and dedifferentiated histologic subtypes was 99% (96–100%) and 70% (55–86%) respectively; none of the 9 patients with myxoid tumors had a distant recurrence at time of last follow-up and 2 of the 4 patients with round cell tumors had distant recurrences. High-grade retroperitoneal LS had a 69% (54–84%) probability free of distant recurrence at 3 years compared with 99% (96–100%) for low-grade tumors. Contiguous organ resection was prognostic for distant recurrence on univariate analysis ($P = 0.02$). Contiguous organ resection was associated a 75% (61–90%) probability free of distant recurrence at 3 years compared with 94% (90–99%) for those patients who did not undergo contiguous organ resection. Of all 99 patients who presented with well-differentiated LS only 3 patients recurred distantly and all 3 were of the sclerosing subtype.

Histologic type and contiguous organ resection were entered into a multivariate Cox proportional hazards model to identify independent predictors of distant recurrence (Table 7). Both factors were significantly associated with distant recurrence by Cox regression analysis: dedifferentiated histology versus well-differentiated (HR 15, $P < 0.0001$) and contiguous organ resection versus no contiguous organ resection (HR 3, $P = 0.02$).

TABLE 5. Predictors of Local Recurrence for Retroperitoneal Liposarcoma From Multivariate Analysis (n = 144)

Variable	Hazard Ratio (95% CI)	*P* Value
Dedifferentiated vs. well differentiated	3.6 (2.2–6.0)	<0.0001
Contiguous organ resection yes vs. no	1.7 (1.02–2.8)	0.04

TABLE 6. Univariate Analysis: Time to Distant Recurrence

	Total	No. of Events	Three-Year Probability Free of Distant Recurrence (95% CI)	*P* Value
Overall	177	19	0.89 (0.84–0.94)	
Variables				
Sex				
Female	69	9	0.86 (0.76–0.95)	0.34
Male	108	10	0.91 (0.85–0.98)	
Age				
Continuous				0.69
<63	88	8	0.91 (0.84–0.97)	0.36
≥63	89	11	0.87 (0.79–0.96)	
Variant				
Well differentiated	99	3	0.99 (0.96–1.0)	<0.0001*
Dedifferentiated	65	14	0.70 (0.55–0.86)	
Myxoid	9	0	–	
Round cell	4	2	–	
Grade				
High	69	16	0.69 (0.54–0.84)	<0.0001
Low	108	3	0.99 (0.96–1)	
Tumor burden continuous				0.85
Margins				
Negative margins	77	7	0.91 (0.83–0.98)	0.33
Positive micro margins	66	8	0.87 (0.78–0.96)	
Positive gross margins	33	4	0.89 (0.75–1)	
Nephrectomy				
No	109	9	0.92 (0.86–0.98)	0.35
Yes	68	10	0.85 (0.75–0.95)	
Contiguous organ resection				
No	130	10	0.94 (0.90–0.99)	0.02*
Yes	47	9	0.75 (0.61–0.90)	
Sclerosing tumor (well-differentiated only)				
No	51	0	–	0.08
Yes	48	3	0.97 (0.92–1)	

*Variables included in multivariate model.

DISCUSSION

LS is the most common mesenchymal tumor of the retroperitoneal space but continues to pose a challenge with regard to diagnosis, prediction of clinical behavior, and treatment of disease recurrence within the abdominal/retroperitoneal space. In the present series, the majority of patients (93%) had tumors of the well-differentiated/dedifferentiated subtypes. Dedifferentiated LS may be particularly difficult to recognize because they exhibit a variable histologic picture, but most frequently they resemble unclassified malignant fibrous histiocytoma (MFH)-like pleomorphic sarcoma or intermediate- to high-grade myxofibrosarcoma.[16,17] Careful and extensive sampling is therefore mandatory, particularly in large retroperitoneal lesions as the well-differentiated component may be overlooked. Primary myxoid/round cell LS are relatively uncommon and account for only 7% of patients with primary retroperitoneal LS. Pleomorphic LS are very rare in the retroperitoneal location and not a single case was found in the present study.

The overall DSS survival of 73% at 3 years and complete resection rate of 81% in this study of primary retroperitoneal LS was similar to the results of other published series of retroperitoneal sarcoma.[10,18–20] Patients with retroperitoneal LS who were treated with incomplete resection had a 3-year DSS of only 43% and thus emphasize the importance of achieving a complete resection even if sacrifice

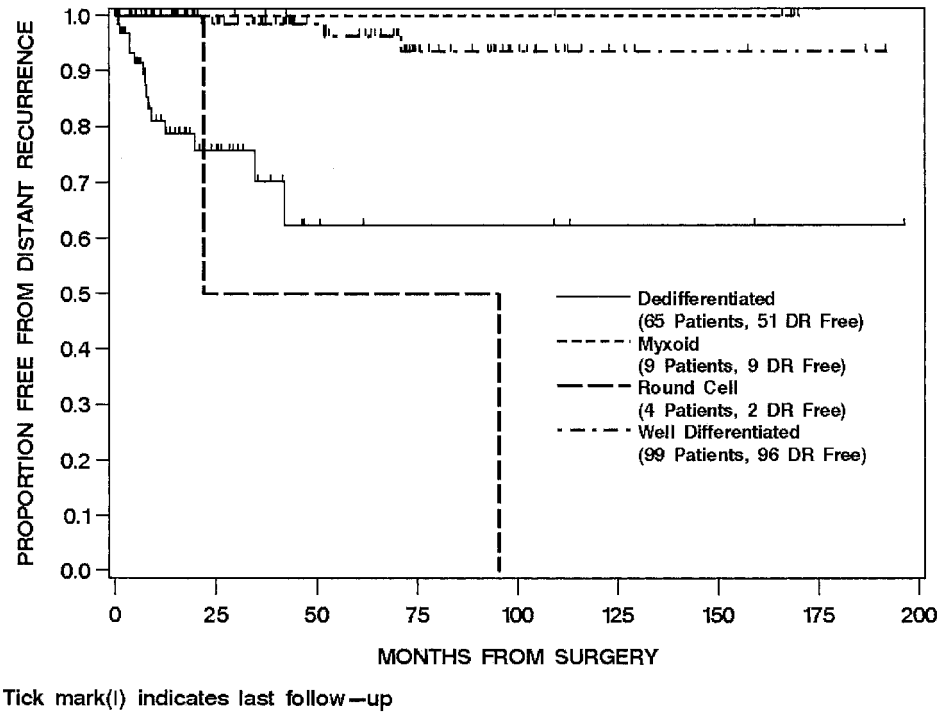

FIGURE 6. Probability free of distant recurrence by histologic subtype.

of a contiguous organ is required. In the present study the 2 most important predictors of DSS on multivariate analysis were histologic subtype (dedifferentiated histology) and the presence of gross positive margins. Whether age was examined as a continuous variable or categorical variable based on the median, older age was associated with a significant reduction in DSS ($P = 0.02$) on univariate analysis. Of interest is that for patients greater than 63 years of age 47% presented with dedifferentiated histology compared with a 32% incidence of dedifferentiation at presentation in the younger age group. In the multivariate analysis when age was analyzed as a categorical variable using the median age of 63 as a cutoff it was not found to be an independent prognostic factor for DSS on multivariate analysis (HR 1.2, $P = 0.43$). This may well be due to the association of age with dedifferentiated histology. However, when age is analyzed as a continuous variable despite adjusting for dedifferentiated histology and gross positive margins age remained a significant prognostic factor on multivariate analysis. Contiguous organ resection was associated with a 2-fold ($P = 0.05$) increased risk of disease-specific death compared with patients not undergoing contiguous organ resection, having adjusted for other prognostic factors. This suggests that involvement of adjacent organs other than kidney portends more aggressive tumor biology for patients with retroperitoneal LS. Tumor burden and nephrectomy had no influence on DSS, suggesting that as long as complete resection can be achieved, these variables do not influence survival in retroperitoneal LS. When we just looked at patients who had a complete resection tumor burden was still not prognostic for DSS. With a median tumor burden of 26 cm, it is evident that the majority of patients with retroperitoneal LS present with tumors >10 cm in size largely because of their deep location. This may suggest that once a retroperitoneal sarcoma exceeds a size of 10 cm that they all behave in a similar high-risk fashion.

TABLE 7. Predictors of Distant Recurrence for Retroperitoneal Liposarcoma From Multivariate Analysis (n = 177)

Variable	Hazard Ratio (95% CI)	*P* Value
Dedifferentiated vs. well differentiated	15.4 (4.2–56.6)	<0.0001
Contiguous organ resection yes vs. no	3.2 (1.2–8.4)	0.02

A previous study of nephrectomy for retroperitoneal sarcoma (all histologic types) demonstrated that renal capsular invasion was present in 15% of patients, renal parenchymal invasion in 9% and renal vein invasion in 3% of patients with the majority of patients 73% having no evidence of direct kidney invasion.[21] Although in the present LS series we did not examine the precise incidence of renal invasion,

the general impression was that LS (particularly the well-differentiated subtype) pushed against adjacent kidney without direct invasion. In such cases our general approach was to strip off the outer capsule of the kidney together with the adjacent LS so that a clean but close margin could be achieved without sacrificing kidney parenchymal function. In cases of LS with circumferential kidney hilar involvement nephrectomy was generally required to achieve a complete resection. The present study demonstrates that kidney preservation with capsular resection was not associated with any reduction in DSS. Thus, nephrectomy should only be performed if required to accomplish a complete gross resection.

Multivariate analysis showed that histologic subtype and contiguous organ resection were independent prognostic factors for local recurrence. Dedifferentiated LS was associated with a 4-fold increased risk of local recurrence compared with well-differentiated histology. In fact, after 3 years of follow-up over 80% of the patients with primary dedifferentiated LS will have recurred locally. Previous studies of retroperitoneal sarcoma have suggested that LS histologic type is associated with a 3-fold higher risk of local recurrence compared with other histologic types that was independent of sarcoma grade.[18] The high rates of local recurrence observed with LS may relate to the often multifocal involvement of disease throughout the retroperitoneal space as well as the difficulty in detecting LS from adjacent normal fat. Of the 99 patients with well-differentiated LS, 39 patients developed at least 1 local recurrence at the time of last follow-up. Of these first-time local recurrences who underwent resection, 83% remained well-differentiated and 17% recurred as high-grade dedifferentiated LS. Of the patients with well-differentiated first local recurrences who then developed a second recurrence, 44% recurred as dedifferentiated LS and 56% remained well differentiated. Thus, the fraction of well-differentiated tumors that progress and dedifferentiate seems to increase with each subsequent recurrence.

Involvement of LS of an adjacent organ other than kidney that requires resection was associated 2-fold higher risk of local recurrence and 3-fold higher risk of distant recurrence compared with those who did not require contiguous organ resection. This suggests the need for contiguous organ resection, excluding kidney relates to the local invasiveness and perhaps multifocal nature of a given LS. In addition, these data suggest that tumors with more extensive local involvement requiring adjacent organ resection are biologically more aggressive and thus are more likely to recur locally as well as distantly.

The most important prognostic factors for distant recurrence include histologic subtype and contiguous organ resection. Multivariate analysis showed that dedifferentiated histology had a 15-fold increased risk of distant recurrence compared with well-differentiated histology. Only 3 of 99 patients with well-differentiated histology recurred distantly and all of these were of the sclerosing subtype. In contrast, 14 of 65 dedifferentiated LS recurred distantly for a probability free of distant recurrence at 3 years of 70% (55–86%). This risk is about 15% higher than generally quoted in the literature[3,12] and may be a result of the fact that our current analysis is on a homogeneous group of patients with primary disease followed in a prospective database with computed scans at defined intervals. The median tumor size of these primary retroperitoneal dedifferentiated LS was 21 cm (5–96 cm). In comparison, the probability free of distant metastasis for all patients with greater than 5-cm, high-grade MFH tumors of the extremity seen at MSKCC from 7/1/82–6/30/02 ($n = 231$) at 3 years is 59%. Thus, despite the large median size of retroperitoneal dedifferentiated LS the risk of distant metastasis appears to be about 10% less at 3 years than the typical high large grade extremity MFH. Longer follow-up on this homogeneous population of dedifferentiated retroperitoneal LS will be needed to determine if with long-term >5-year follow-up the patients continue to develop distant metastasis and in the end approach the same distant recurrence rates as seen for the typical large, high-grade nonlipogenic extremity tumor.

CONCLUSIONS

In this study of patients with retroperitoneal LS, histologic subtype, incomplete resection, contiguous organ resection (excluding nephrectomy) and increasing age are strongly associated with death from tumor. Tumor burden and nephrectomy were not associated with disease specific survival. Surgical treatment of retroperitoneal LS should consist of an aggressive approach to achieve a complete surgical resection. En bloc resection of adjacent organs should be performed if necessary to achieve a complete resection. However, kidney parenchymal sparing renal capsular resections can be performed without any measurable influence on DSS as long as complete resection is achieved. Despite an aggressive surgical approach over 80% of patients with dedifferentiated histology will recur locally and 30% will metastasize to distant sites within 3 years of diagnosis. Combination of surgery with new systemic therapies, such as PPARγ ligands, and locoregional therapies, such as preoperative intensity modulated radiation therapy, are needed to improve outcomes in patients with retroperitoneal LS. The prognostic variables and outcome data generated from the present study should serve as the "benchmark" for future trials in retroperitoneal LS as no patients received chemotherapy and only 8% of patients were treated with adjuvant radiotherapy. In addition, this work emphasizes the importance of stratification by

histology and histologic subtype in the design of future prospective randomized trials in retroperitoneal sarcoma.

REFERENCES

1. Mack T. Sarcomas and other malignancies of soft tissue, retroperitoneum, peritoneum, pleura, heart, mediastinum and spleen. *Cancer*. 1995;75:211–244.
2. Fletcher CM, Akerman P, Cin I, et al. Correlation between clinical pathological features and karyotype in lipomatous tumors. *Am J Pathol*. 1996;148:623–630.
3. Henricks WH, Chu YC, Goldblum JR, et al. Dedifferentiated liposarcoma: a clinicopathological analysis of 155 cases with a proposal for an expanded definition of dedifferentiation. *Am J Surg Pathol*. 1997;21: 271–81.
4. Linehan DC, Lewis JJ, Leung D, et al. Influence of biologic factors and anatomic site in completely resected liposarcoma. *J Clin Oncol*. 2000; 18:1637–1643.
5. Lewis J, Leung D, Woodruff J, et al. Retroperitoneal soft-tissue sarcoma. *Ann Surg*. 1998;228:355–365.
6. Rosai J, Akerman M, Dal Cin P. Morphologic-karyotypic study of 59 atypical lipomatous tumors: evaluation of their relationship and differential diagnosis with other adipose tissue tumors. *Am J Surg Pathol*. 1996;20:1182–1189.
7. McCormick D, Mentzel T, Beham A, et al. Dedifferentiated liposarcoma: clinicopathologic analysis of 32 cases suggesting a better prognostic subgroup among pleomorphic sarcomas. *Am J Surg Pathol*. 1994;18:1213–1223.
8. Antonescu CR, Tschernyavsky SJ, Decuseara R, et al. Prognostic impact of P53 status, TLS-CHOP fusion transcript structure, and histological grade in myxoid liposarcoma: a molecular and clinicopathologic study of 82 cases. *Clin Cancer Res*. 2001;7:3977–3987.
9. Gebhard S, Coindre JM, Michels JJ, et al. Pleomorphic Liposarcoma: clinicopathologic, immunohistochemical, and follow-up analysis of 63 cases: a study from the French Federation of Cancer Centers Sarcoma Group. *Am J Surg Pathol*. 2002;26:601–616.
10. 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.
11. Patel SR, Vadhan-Raj S, Papadopolous N, et al. High-dose ifosfamide in bone and soft tissue sarcomas: results of phase II and pilot studies–dose-response and schedule dependence. *J Clin Oncol*. 1997;15:2378–2384.
12. Fletcher C, Unni K, Mertens F, eds. Pathology and genetics of tumors of soft tissue and bone. In: Kleihues P, Sobin L, eds. *World Health Organization Classification of Tumors, Vol. 4*. Lyon, France: International Agency for Research on Cancer Press; 2002:427.
13. Mantel N. Evaluation of survival data and two new rank order statistics arising in its consideration. *Cancer Chemother Rep*. 1966;50:163–170.
14. Cox D, Oakes D. *Analysis of Survival Data*. 1st ed. New York: Chapman and Hall; 1990.
15. Kaplan E, P. Meier. Nonparametric estimation from incomplete observations. *J Am Statist Assoc*. 1958;53:457–481.
16. Weiss SW, Rao VK. Well-differentiated liposarcoma (atypical lipoma) of deep soft tissue of the extremities, retroperitoneum, and miscellaneous sites. A follow-up study of 92 cases with analysis of the incidence of "dedifferentiation". *Am J Surg Pathol*. 1992;16:1051–1058.
17. Mentzel T, Fletcher C. Lipomatous tumors of soft-tissues: an update. *Virchows Arch*. 1995;427:353–363.
18. Lewis JJ, Leung D, Woodruff JM, et al. Retroperitoneal soft-tissue sarcoma: analysis of 500 patients treated and followed at a single institution. *Ann Surg*. 1998;228:355–365.
19. Storm FK, Eilber FR, Mirra J, et al. Morton, Retroperitoneal sarcomas: a reappraisal of treatment. *J Surg Oncol*. 1981;17:1–7.
20. Karakousis CP, Velez AF, Gerstenbluth R, et al. Resectability and survival in retroperitoneal sarcomas. *Ann Surg Oncol*. 1996;3:150–158.
21. Russo P, Kim Y, Ravindran S, et al. Nephrectomy during operative management of retroperitoneal sarcoma. *Ann Surg Oncol*. 1997;4:421–424.

Discussions

DR. RAPHAEL E. POLLOCK (Houston, Texas): I appreciate having had the opportunity to review the manuscript prior to this meeting and appreciate the privilege of the floor at this time. A couple of thoughts:

First of all, it is clear on the basis of this work that the surgical services at Sloan-Kettering can continue to successfully engraft organ transplants from Boston to New York; congratulations to both Dr. Singer and Dr. Brennan.

This is a very important study. We are considering a very rare disease treated in a standard fashion at 1 institution that is intimately familiar with the disease and its natural history. The patients reported on here have all been followed prospectively after having been treated in a standard fashion. And I think it does show the value of prospective data collection, because it suggests that in some circumstances histologic subtype may be a or even the critical driver in terms of multiparametric patient outcomes.

Dr. Singer has demonstrated that differentiated pathologies have a very different behavior than do de-differentiated: the bottom line is a 4-fold increase in local recurrence in de-differentiated patients; as a matter of fact, after 3 years, 80% of the de-differentiated patients will have local occurrence. So my questions really focus on how we might use this information rather than the basis of its derivation per se. I have 3 brief interrelated questions:

First: Given the differing biologies under consideration, how does 1 justify adjacent non-nephrectomy organ resection in de-differentiated patients if they are doomed to local recurrence anyway? Or, on the other hand, if well-differentiated patients behave in such an indolent fashion, is there any role for subtotal debulking prospective palliation strategies in these individuals?

The second question is: Given the biologic impact of de-differentiated versus well-differentiated histology, as a routine practice do you biopsy areas of suspected de-differentiation either pre or intraoperatively, and as a practical matter how do you make use of the knowledge of de-differentiated status? For example, does this drive you to neoadjuvant chemo- or radiotherapy approaches? Does it govern the extent of resection? Or does it lead you to recruit or think about recruiting intraoperative radiotherapy or other such intraoperative strategies?

And the third question, which really ties directly to this, is: Do you use intraoperative frozen section as a guide to the extent of resection, particularly in non-nephrectomy contiguous organ resection in de-differentiated patient?

This is a critically important study because it has the potential to change our approach to a very devastating oncology problem, and I appreciate the opportunity to pose these questions this morning. Thank you.

DR. SAMUEL SINGER (New York, New York): Thank you, Dr. Pollock. In terms of the issue of how the data presented would change our approach to retroperitoneal sarcoma and how we would use this information in treating patients. Basically, I see that there are 3 potential uses of this information. The first 1 is that there is now a significant problem with consistently grading these tumors even by experienced pathologists after having the entire specimen to review. So the idea would be to use molecular genetics combined with morphology to see if we can more objectively grade these tumors to assess a patient's risk of local and distant relapse.

Second, by understanding the underlying biology of each histologic subtype we can figure out which patients, for example, with well-differentiated liposarcoma at high risk to dedifferentiate to a dedifferentiated liposarcoma of higher grade; in other words which of these patients would progress to a more aggressive form in the future. Thirdly, this data on histologic subtype can serve as a benchmark for future trial designs in terms of assessing high-risk groups for both local and distant recurrence. This data will permit us to identify how we should stratify patients in these randomized trials so as to optimize their design and accurately balance risk in each arm.

To address the second question of whether our operative approach would change based on histologic subtype. For example, would our operative approach for organ preservation and kidney sparing nephrectomy change based on histologic subtype (whether it was well-differentiated or dedifferentiated). We would strive for a complete resection of all gross disease independent of the histologic subtype. In kidney sparing resections, most often the kidney parenchyma is not involved and you can often excise the kidney capsule with the adjacent tumor (for a clean but close margin) whether it is well-differentiated or dedifferentiated. If the renal hilum is involved with either well-differentiated or dedifferentiated tumor then 1 will need to completely remove the kidney to achieve a complete resection of all liposarcoma. We would follow the same approach for other contiguous organ resections. If there is obvious organ involvement then that needs to be resected regardless of the histologic subtype. Occasionally it is required that 1 do a contiguous organ resection for exposure so that 1 may obtain a complete resection but again this is typically unrelated to the histologic subtype. Finally, often when you take out these very large liposarcomas there is no way of knowing whether there is a section of the tumor, which has dedifferentiated until you have completely removed it.

A third question was whether there is value in doing an intraoperative frozen section analysis. In general frozen section analysis of fatty tissue is not particularly useful. It is very hard to freeze fat without significant artifact and obtain an accurate histologic diagnosis. Accurate histologic analysis on frozen section is extremely difficult for well-differentiated lipoma like and sclerosing liposarcoma given their high fat content. For dedifferentiated high-grade sarcomas with less fat content frozen section is more accurate. We are presently working in our laboratory using magic angle spinning and NMR spectroscopy techniques on fresh tissue specimens to do real time analysis of normal fat versus well-differentiated liposarcoma to see if we can accurately distinguish tumor fat from normal fat. In this analysis, we are looking for biochemical differences between normal fat and liposarcoma. We want to see whether we can in a blinded fashion compare biochemical analysis of the same specimen used for NMR to morphology on permanent histologic sections to see how accurate we can do this in real time. However, presently we do not have the capability yet of doing intraoperative frozen sections accurately on these tumors that contain high levels of fat. We are also working on developing molecular genetic techniques in real time for diagnostic analysis of these liposarcomas.

The fourth question is how we would make practical use of knowing that a patient had dedifferentiated histology preoperatively and whether this would alter our choice of adjuvant therapy and the extent of resection. In my experience dedifferentiated liposarcomas are not particularly responsive to neo-adjuvant chemotherapy and at present we have no protocols for that at Memorial and so if we knew an area was dedifferentiated we would not treat that patient with neo-adjuvant chemotherapy. In the past, it was believed that the systemic risks from these dedifferentiated liposarcomas, even though they were high grade was relatively low and they were mainly prone to local recurrence problems with a distant recurrence rate of only 15%. In the present study we show that the distant recurrence risk is as high as 30% and thus it would not be unreasonable to consider potential systemic therapy in future trials. This has not been our practice to date. In terms of extent of resection again our goal would be complete resection and that would not change whether it was well-differentiated or dedifferentiated. You are only as good as your most limited margin and so extended organ resection to achieve more than a complete resection is usually not indicated unless it is needed to make sure that you have removed all gross tumor. Brachytherapy techniques have been associated with high morbidity in our hands and so we have not used those. We now plan to examine the role of preoperative IMRT radiotherapy at Memorial in a randomized trial in patients with primary retroperitoneal liposarcoma. In this trial, patients would be stratified by histologic subtype, which clearly will be important in analyzing the results and balancing treatment arms in the trial. The primary end point would be local recurrence free survival. The idea being if we could improve local recurrence free survival for both the well-differentiated and dedifferentiated tumors then that would prove overall survival as well in these patients where they primarily die of local control problems in the abdomen and retroperitoneum.