

Symptoms at diagnosis as independent prognostic factors in retroperitoneal liposarcoma

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Abstract. The prognostic factors of retroperitoneal liposarcoma have yet to be clearly determined due to its rarity, whereas the prognostic value of symptoms at diagnosis has never been evaluated to date. In this context, we reviewed 24 consecutive patients with primary retroperitoneal liposarcoma who underwent surgical resection with curative intent at our institution. The Kaplan-Meier analysis and the log-rank test were used to estimate progression-free survival (PFS; primary endpoint) and sarcoma-specific survival (SSS; secondary endpoint). The effect of various clinicopathological factors, including symptoms at diagnosis, on these two endpoints was assessed with a Cox proportional hazards model. During the study period, 11 patients (45.8%) developed recurrence after the initial surgery and 8 (33.3%) succumbed to retroperitoneal liposarcoma, with a median follow-up of 64 months. A total of 16 patients (66.7%) had symptoms at diagnosis, while the remaining 8 (33.3%) were diagnosed incidentally. The symptoms were palpability of the tumor (n=8); abdominal pain/fullness (n=3); flank pain/fullness (n=2); lower extremity pain (n=1); testicular pain due to varicocele (n=1); and discomfort on urination (n=1). Patients with symptoms at diagnosis were significantly more likely to develop recurrence (log-rank test, P=0.0196) and were also more likely to succumb to sarcoma (P=0.0778) compared with asymptomatic patients. On the multivariate analysis, symptoms at diagnosis and dedifferentiated components were independent predictors of poor PFS, while positive surgical margins were predictors of poor SSS. Given that symptoms at diagnosis are easily accessible for physicians, they may prove to be useful additional prognostic factors for primary retroperitoneal liposarcoma.

Introduction

Retroperitoneal sarcomas, or retroperitoneal soft tissue sarcomas, are rare mesenchymal tumors accounting for ~0.15% of all malignancies (1,2). Retroperitoneal sarcomas display a vast array of histological subtypes, among which liposarcomas are the most common (30-50%), followed by leiomyosarcomas and malignant fibrous histiocytomas, also referred to as undifferentiated pleomorphic sarcomas, according to the updated World Health Organization (WHO) classification of soft tissue tumors (1,3). Retroperitoneal liposarcoma typically presents as advanced disease and often carries a poor prognosis (4). However, its rarity means that its prognostic factors are poorly understood. Furthermore, the majority of previously published series on primary malignant retroperitoneal tumors have included retroperitoneal liposarcomas together with other retroperitoneal sarcomas with heterogeneous histologies, thus preventing the independent characterization of this specific subtype (3,5-8).

Retroperitoneal liposarcomas usually present as an asymptomatic abdominal mass, incidentally detected during abdominal examination or abdominal imaging studies performed for other purposes, while others are detected due to the presence of clinical symptoms (4). Although symptoms at diagnosis have been identified as prognostic markers in several malignancies (9-12), their prognostic value for retroperitoneal liposarcoma has yet to be evaluated. In this study, we assessed the prognostic factors in primary retroperitoneal liposarcoma, focusing on the presence or absence of clinical symptoms at diagnosis.

Patients and methods

Patients and clinicopathological factors. A total of 24 consecutive patients with primary retroperitoneal liposarcomas who underwent surgical resection with curative intent at our institution (Graduate School of Medicine, The University of Tokyo, Tokyo, Japan) between 1985 and 2014 were reviewed. This study was approved by the internal Institutional Review Board.

Regarding pathological factors, a single pathologist (T.M.) reviewed all the slides of the surgical specimens. Tumor size was defined as the maximum diameter of the tumor at pathological analysis. The patients were followed up until March, 2015.

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Statistical analysis. The Kaplan-Meier analysis and the log-rank test were used to estimate progression-free survival (PFS; primary endpoint) and sarcoma-specific survival (SSS; secondary endpoint) after initial surgery. The effect of various clinicopathological factors, including symptoms at diagnosis, on these two endpoints was assessed with univariate and multivariate Cox proportional hazards analyses. For the multivariate analysis, a backward stepwise procedure (entry, 0.05; removal, 0.10) was selected, due to the small sample size. All the statistical analyses were performed using JMP Pro software, version 11.0.0 (SAS Institute, Cary, NC, USA). $P < 0.05$ was considered to indicate statistically significant differences.

Results

Patient characteristics. The 24 patients included 14 men (58.3%) and 10 women (41.7%), with a median age of 59 years (range, 40-79 years) at initial surgery. A total of 11 patients (45.8%) developed recurrence after the initial surgery, and 8 (33.3%) succumbed to retroperitoneal liposarcoma during the study period, with a median follow-up of 64 months (range, 2-225 months) (Table I).

Symptoms at diagnosis. A total of 16 patients (67%) had symptoms at diagnosis, while the remaining 8 (33%) were diagnosed incidentally. The symptoms included palpability of the tumor in 8 patients; abdominal pain/fullness in 3; flank pain/fullness in 2; lower extremity pain in 1; testicular pain due to varicocele in 1; and discomfort on urination in 1 patient. Regarding the last 3 cases, the lower extremity pain was attributed to neural invasion by the tumor; varicocele to tumor infiltration of the left gonadal vein; and discomfort on urination to tumor infiltration of the urinary bladder. Preoperative dynamic contrast-enhanced magnetic resonance imaging in the last patient is shown in Fig. 1, demonstrating tumor infiltration of the urinary bladder, which may have caused the discomfort on urination. Of the 8 asymptomatic patients, 5 were incidentally diagnosed with retroperitoneal liposarcoma during a follow-up visit for another condition, and 3 were diagnosed during a periodic check-up for cancer.

Tumor characteristics. The median tumor size was 19.0 cm (range, 11.5-32.0 cm). All the patients had tumors sized >10 cm, and all patients with symptoms at diagnosis had tumors sized >15 cm. The predominant histological subtypes were well-differentiated liposarcoma (atypical lipomatous tumor) in 19 (79.2%); myxoid liposarcoma in 3 (12.5%); and dedifferentiated liposarcoma in 2 patients (8.3%). Pathological analysis was performed according to the updated WHO classification of soft tissue tumors. A total of 8 patients (33.3%) had dedifferentiated sarcoma components in their surgical specimens and 17 patients (70.8%) had microscopically positive resection margins.

PFS and SSS in patients with and without symptoms at diagnosis. The Kaplan-Meier curves depicting PFS and SSS in patients with and without symptoms at diagnosis are presented in Fig. 2. The patients with symptoms at diagnosis were significantly more likely to develop recurrence (log-rank test, $P=0.0196$, Fig. 2A) and more likely to succumb to sarcoma ($P=0.0778$, Fig. 2B) compared with asymptomatic patients.

Table I. Patient characteristics (n=24).

Characteristics	Values
Gender, no. (%)	
Male	14 (58.3)
Female	10 (41.7)
Median age at initial surgery, years (range)	59 (40-79)
Body mass index, kg/m ² , median (range)	23.4 (17.1-35.6)
Clinical symptoms at diagnosis, no. (%)	16 (66.7)
Incidental tumor, no (%)	8 (33.3)
Median tumor size at initial surgery, cm (range)	19.0 (11.5-32.0)
Dominant histological subtype, no. (%)	
Well-differentiated liposarcoma	19 (79.2)
Myxoid liposarcoma	3 (12.5)
Dedifferentiated liposarcoma	2 (8.3)
Presence of dedifferentiated components, no. (%)	8 (33.3)
Positive surgical margins, no. (%)	17 (70.8)
Adjuvant chemotherapy, no. (%)	5 (20.8)
Median follow-up, months (range)	64 (2-225)

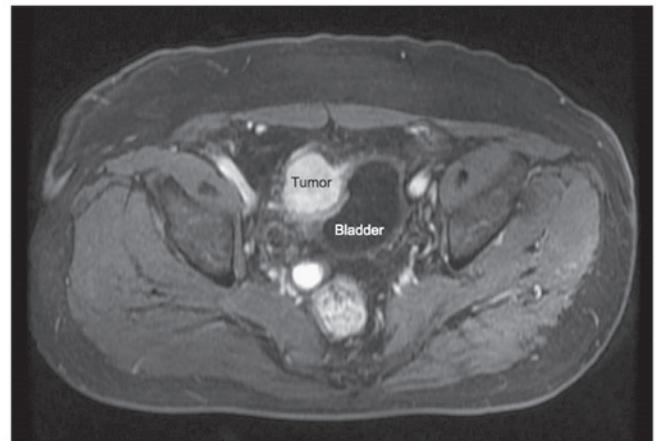


Figure 1. Dynamic contrast-enhanced magnetic resonance image of a patient who presented with discomfort on urination at the initial visit. The image demonstrates tumor infiltration of the urinary bladder, which may have been responsible for the symptoms.

Effect of clinicopathological factors on PFS. The univariate analysis demonstrated that symptoms at diagnosis, dedifferentiated components and positive surgical margins were all associated with poor PFS, whereas in the multivariate analysis, the presence of symptoms at diagnosis [hazard ratio (HR)=6.134, $P=0.0347$] and dedifferentiated components (HR=4.809, $P=0.0337$) were identified as independent predictors of poor PFS (Table II). The details of this multivariate analysis using the backward stepwise procedure were as follows: For the first step, all three univariately significant factors (symptoms at diagnosis, dedifferentiated components and surgical margins) were entered in the multivariate analysis,

Table II. Univariate and multivariate analyses of the effect of clinicopathological factors on progression-free survival after the initial surgery.

Factors	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Gender				
Male vs. female	1.506 (0.449-5.813)	0.5119		
Age at initial surgery				
>59 vs. ≤59 years ^a	0.695 (0.182-2.310)	0.5572		
Body mass index				
>23.4 vs. ≤23.4 kg/m ^{2a}	0.782 (0.223-2.638)	0.6886		
Symptoms at diagnosis				
Yes vs. no	7.782 (1.481-143.0)	0.0114 ^b	6.134 (1.118-114.4)	0.0347 ^b
Tumor size				
>19 vs. ≤19 cm ^a	2.418 (0.726-9.271)	0.1506		
Dedifferentiated components				
Yes vs. no	5.890 (1.501-28.87)	0.0111 ^b	4.809 (1.126-27.25)	0.0337 ^b
Surgical margins				
Positive vs. negative	9.220 (1.685-172.1)	0.0070 ^b		
Adjuvant chemotherapy				
Yes vs. no	2.528 (0.656-8.481)	0.1647		
Leukocyte count				
>6,200 vs. ≤6,200 cells/ μ l ^a	1.059 (0.314-3.719)	0.9255		
Neutrophil-to-lymphocyte ratio				
>2.3 vs. ≤2.3 ^a	1.371 (0.410-4.782)	0.6035		
Lymphocyte-to-monocyte ratio				
>3.6 vs. ≤3.6 ^a	1.425 (0.428-5.462)	0.5684		
Hemoglobin				
>13 vs. ≤13 g/dl ^a	1.037 (0.298-3.453)	0.9525		
Albumin				
>3.9 vs. ≤3.9 g/dl ^a	0.590 (0.153-1.980)	0.3964		
Lactate dehydrogenase				
Using actual values (per 10 IU/l increase)	0.929 (0.811-1.061)	0.2744		
Alkaline phosphatase				
Using actual values (per 10 IU/l increase)	1.050 (0.906-1.222)	0.5159		
C-reactive protein				
>0.3 vs. ≤0.3 mg/dl	0.873 (0.250-2.919)	0.8229		

^aMedian. ^bStatistically significant. HR, hazard ratio; CI, confidence interval.

and surgical margins, which had the highest P-value (0.2139) were eliminated. Subsequently, the remaining two factors were entered in the analysis, and this was considered as the final model, as both had statistically significant P-values (<0.05).

Effect of clinicopathological factors on SSS. Dedifferentiated components and positive surgical margins were associated with poor SSS in the univariate analyses, whereas positive surgical margins were found to be an independent predictor of poor SSS in the multivariate analysis (Table III). However, the HR for positive surgical margins did not converge, possibly

due to few events; therefore this result is only suitable for reference purposes. The presence of symptoms at diagnosis exhibited a non-significant trend for poor SSS in the univariate analysis (P=0.0577).

Discussion

In the present study, the presence of symptoms at diagnosis in patients with primary retroperitoneal liposarcoma was an independent predictor of poor PFS, and tended to be associated with poor SSS. To the best of our knowledge, this is the first

Table III. Univariate and multivariate analyses of the effect of clinicopathological factors on sarcoma-specific survival after the initial surgery.

Factors	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Gender				
Male vs. female	1.893 (0.455-9.381)	0.3804		
Age at initial surgery				
>59 vs. ≤59 years ^a	0.608 (0.088-2.693)	0.5319		
Body mass index				
>23.4 vs. ≤23.4 kg/m ^{2a}	1.306 (0.300-5.650)	0.7118		
Symptoms at diagnosis				
Yes vs. no	5.691 (0.952-109.0)	0.0577		
Tumor size				
>19 vs ≤19 cm ^a	3.215 (0.649-23.67)	0.1568		
Dedifferentiated components				
Yes vs. no	15.26 (2.108-307.6)	0.0062 ^b	7.088 (0.989-143.1)	0.0525
Surgical margins				
Positive vs. negative	NC	0.0011 ^b	NC	0.0084 ^b
Adjuvant chemotherapy				
Yes vs. no	3.510 (0.647-19.07)	0.1370		
Leukocyte count				
>6,200 vs. ≤6,200 cells/ μ l ^a	0.376 (0.565-13.98)	0.2103		
Neutrophil-to-lymphocyte ratio				
>2.3 vs. ≤2.3 ^a	1.954 (0.438-13.53)	0.3968		
Lymphocyte-to-monocyte ratio				
>3.6 vs. ≤3.6 ^a	0.532 (0.124-2.284)	0.3815		
Hemoglobin				
>13 vs. ≤13 g/dl ^a	0.805 (0.164-3.316)	0.7661		
Albumin				
>3.9 vs. ≤3.9 g/dl ^a	0.622 (0.126-2.571)	0.5130		
Lactate dehydrogenase				
Using actual values (per 10 IU/l increase)	0.932 (0.798-1.090)	0.3669		
Alkaline phosphatase				
Using actual values (per 10 IU/l increase)	1.130 (0.942-1.368)	0.1853		
C-reactive protein				
>0.3 vs. ≤0.3 mg/dl	1.306 (0.301-5.644)	0.7117		

^aMedian. ^bStatistically significant. HR, hazard ratio; CI, confidence interval; NC, not converged.

assessment of the prognostic value of symptoms at diagnosis in patients with retroperitoneal liposarcoma.

The rarity of retroperitoneal liposarcoma means that its prognostic factors have yet to be clearly determined. Furthermore, the majority of previous studies on primary malignant retroperitoneal tumors have included patients with other retroperitoneal sarcomas with heterogeneous histologies together with retroperitoneal liposarcomas, thus preventing independent characterization (3,5-8). However, a limited number of studies have specifically investigated retroperitoneal liposarcomas. Singer *et al* (13) retrospectively reviewed

177 patients with primary retroperitoneal liposarcoma and demonstrated that dedifferentiated histology (HR=4, P<0.0001) and contiguous organ resection (HR=2, P=0.04) were significantly associated with PFS according to the Cox regression analysis, while dedifferentiated histology (HR=6, P<0.0001), gross positive margins (HR=4, P<0.0001), contiguous organ resection (HR=2, P=0.05) and age (HR=1.03, P=0.03) were significantly associated with SSS. A recent comprehensive review of retroperitoneal liposarcomas also reported that the most consistent prognostic factor was completeness of surgical resection, with negative margins (4). Our results supported

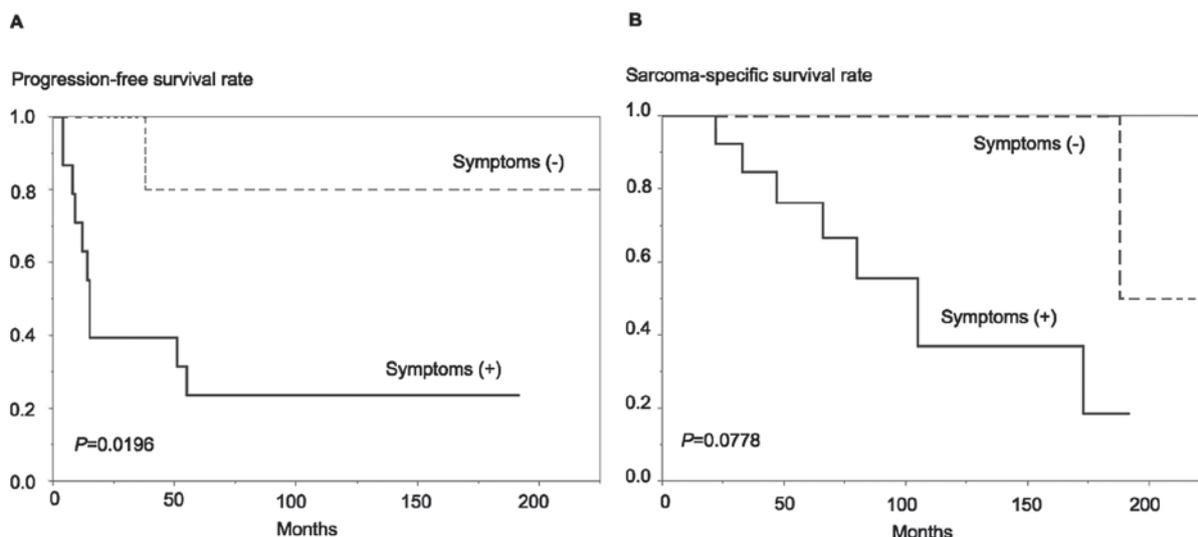


Figure 2. Kaplan-Meier curves depicting (A) progression-free survival and (B) sarcoma-specific survival in patients with and without symptoms at diagnosis (log-rank test: $P=0.0196$ for progression-free survival; and $P=0.0778$ for sarcoma-specific survival).

these findings, given that the univariate analysis revealed an association of dedifferentiated components and positive surgical margins with both PFS and SSS, while the multivariate analysis identified the presence of positive surgical margins as an independent predictor of SSS.

Regarding the presence of symptoms, we were only able to find one study that evaluated the prognostic impact of symptoms on survival in retroperitoneal sarcoma. In a review of 49 patients with primary malignant retroperitoneal tumors, including 25 (51%) with liposarcomas (6), 44 patients (90%) had symptoms, but these were not associated with overall survival ($P=0.282$, log-rank test).

By contrast, several studies have investigated the prognostic value of tumor size in malignant retroperitoneal tumors (5-8,13), mostly using a cut-off value of 10 cm, particularly in studies conducted over a decade ago (5-7). A relatively small-scale ($n=49$) study reported a prognostic value of tumor size >10 cm (6), whereas another larger ($n=500$) study did not report such an association (7). More recently, in a review of 1,091 patients with soft tissue sarcoma of any primary site (including extremities, trunk and retroperitoneum), Lahat *et al* (14) demonstrated that patients with tumors sized >15 cm were at increased risk of developing distant recurrence and exhibited higher disease-specific mortality compared with those with smaller tumors; they suggested that tumor size should be revised in the current American Joint Committee on Cancer (AJCC) staging system used for soft tissue sarcomas. The AJCC system currently uses a 5-cm threshold, which is better suited for extremity sarcomas, but has limited discriminative power for retroperitoneal liposarcomas, almost all of which are >5 cm (4,15). Indeed, all the patients in the present study had tumors >10 cm (median, 19.0 cm), and tumor size was not associated with PFS or SSS.

The mechanisms underlying the association between symptoms at diagnosis and poor outcome in patients with retroperitoneal liposarcomas may be associated with the fact that an aggressive tumor may be recognized by the host more easily than an indolent one. The most common symp-

toms (13/16, 81%) in the present study were palpability of the tumor and pain/fullness of the abdomen/flank, as previously reported (3). In the case of two tumors of the same size but with different growth rates, the faster-growing tumor (i.e., more aggressive tumor) would be more likely to cause pain/fullness compared with the slower-growing tumor, due to the greater change. However, tumor size itself is also an important factor, which is supported by the fact that all the symptomatic patients in our cohort had tumors sized >15 cm. In addition to growth rate and tumor size, local invasion of the retroperitoneal structures may cause neurological, musculoskeletal and urinary/bowel symptoms (4), which are also considered to be specific characteristics of aggressive tumors. Of the 16 (19%) symptomatic patients in our cohort, 1 had lower extremity pain due to neural invasion, 1 had testicular pain due to varicocele as a consequence of tumor infiltration of the left gonadal vein, and 1 presented with discomfort on urination due to tumor infiltration of the urinary bladder. Since several inflammatory markers, such as neutrophil-to-lymphocyte ratio, lymphocyte-to-monocyte ratio and C-reactive protein, have been reported to be prognostic factors in soft tissue sarcomas (16-19), we also evaluated certain laboratory parameters; however, none were found to be associated with prognosis in the present study (Tables II and III).

This study was limited by its retrospective design and small sample size. Therefore, further confirmatory studies with larger populations are required to validate these results. However, these preliminary results suggest that the presence of symptoms at diagnosis may be an easily available, useful prognostic factor to complement existing markers in retroperitoneal liposarcoma.

In conclusion, retroperitoneal liposarcomas diagnosed by clinical symptoms are associated with a poorer prognosis compared with incidentally diagnosed retroperitoneal liposarcomas. Furthermore, the presence of symptoms at diagnosis was found to be an independent predictor of PFS, which may prove to be a useful additional prognostic factor in primary retroperitoneal liposarcoma.

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