



Optimal maximum duration for delaying salvage operation when recurrence of retroperitoneal liposarcoma is suspected: a single-center study

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Abstract

Background This study was designed to identify the optimal maximum duration for delaying salvage operation when recurrence of retroperitoneal liposarcoma (LPS) is suspected.

Methods Patients who underwent salvage operation at Samsung Medical Center for recurrent retroperitoneal LPS from January 2000 to December 2015 were reviewed. The time interval between recurrence and operation for recurrence was divided by 1, 2 or 3 months. A Cox proportional-hazards model was used to analyze factors related to disease-free survival along with recurrence-to-operation interval divided by 1, 2 or 3 months.

Results The 1-, 3-, and 5-year disease-free survival rates were 43.2%, 15.6% and 13.4%, respectively. FNCLCC grade ($p=0.023$) and recurrence-to-operation interval divided by 3 months ($p=0.003$) were significant factors associated with recurrence. FNCLCC grade 2 (HR 1.940, CI 0.935–4.026, $p=0.238$) and grade 3 (HR 4.049, CI 1.767–9.281, $p=0.007$) showed increased risk compared to grade 1. Patients who underwent salvage operation more than 3 months after recurrence showed significantly increased risk of recurrence compared to patients within 3 months (HR 2.724, CI 1.391–5.337, $p=0.003$).

Conclusions Based on our analysis of recurrence-free survival, salvage operation can be delayed for less than 3 months when recurrence is suspected. A short-term follow-up imaging study should be performed within this period.

Keywords Retroperitoneal liposarcoma · Retroperitoneal soft tissue sarcoma · Recurrent retroperitoneal liposarcoma

Abbreviations

LPS	Liposarcoma
STS	Soft tissue sarcoma
CT	Computed tomography
RT	Radiotherapy
FNCLCC	Fédération Nationale des Centres de Lutte Contre le Cancer

Introduction

Liposarcoma (LPS) is the most common type among retroperitoneal sarcoma, followed by leiomyosarcoma [1]. LPS occurs wherever fat is located, and about 35% of retroperitoneal LPSs originate in perirenal fat [2]. Due to large potential spaces in the retroperitoneum, LPS and other soft tissue sarcomas (STSs) can grow into giant tumors without any recognizable symptoms or signs. These retroperitoneal STSs are discovered with an average diameter of > 20 cm [3].

The most effective treatment for retroperitoneal STS, including LPS, is surgical removal. Several studies have proposed that failure to attain negative surgical margins or tumor invasion is a negative prognostic factor for recurrence [4]. Superior survival with complete removal often requires en-bloc resection including contiguous adjacent organs, such as the kidneys, adrenals, pancreas, small bowel, and colon [5, 6]. To overcome the surgical difficulty of achieving complete surgical resection, some authors have proposed performing compartmental resection [7, 8]. Despite the trend

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toward improving results with aggressive surgeries, local tumor recurrence is frequent compared to other malignancies [7, 9–14].

Computed tomography (CT) is the most popular modality for diagnosing and assessing the invasiveness of retroperitoneal STS [15]. Postoperative follow-up CT scans are also frequently performed to screen remnant or recurrent tumors. In our institution, postoperative CT scans are routinely obtained 1 week, 3 months and 6 months after the operation. In some occasions, CT scans do not give conclusive information. Some suspicious findings are actually normal postoperative change or non-growing fat tissue, while some suspicious findings increase in size on consecutive imaging study. For oncologists who face a suspicious but not conclusive finding on postoperative CT scans, clinical decision-making is a difficult task. This study is designed to determine the optimal maximum duration for delaying salvage operation when recurrence of retroperitoneal LPS is suspected on postoperative CT.

Materials and methods

Patients

Patients who underwent surgery at Samsung Medical Center for recurrent retroperitoneal LPS from January 2000 to December 2015 were retrospectively reviewed. Patients with incomplete gross resection in the previous operation were excluded. When a patient underwent several operations for recurrent retroperitoneal LPS, the first operation performed at our center was included for analysis. Therefore, patients who experienced recurrence after a previous operation at other medical centers were also included in the study.

Data collection

Data on patient demographics, previous operations and history of recurrence were reviewed. Recurrence data related to the first operation performed at our center were assessed. To simplify descriptions of the first operation performed at our center for recurrence, these procedures will be called “salvage operation”. Surgical factor data such as resected organs and completeness of resection were collected based on operation records. Size and number of recurrent tumors, histologic differentiation, FNCLCC (Fédération Nationale des Centres de Lutte Contre le Cancer) grade of both recurrent tumor and tumor from previous operation, margin status, and the presence of organ invasion were assessed. Data on radiotherapy (RT) both after the previous operation and the salvage operation were also collected.

Data analysis

The time point for recurrence was set as the first time when imaging findings were suspicious for recurrence. Even when findings were suspicious but not definite for recurrence, the first time the finding was observed was set as the time of recurrence if the finding was confirmed as a recurrent tumor on the concurrent CT scan.

To identify the optimal maximum duration for delaying salvage operation when follow-up CT scan is not conclusive for recurrence, the time interval between recurrence and operation for recurrence was divided by 1, 2 or 3 months. Performance of nephrectomy was divided into no nephrectomy, nephrectomy during previous operation, and nephrectomy during salvage operation for recurrence. Radiotherapy was divided into no radiotherapy, radiotherapy after previous operation and radiotherapy after salvage operation for recurrence.

Kaplan–Meier survival was used to estimate 1-, 3-, and 5-year disease-free survival. A Cox proportional-hazards model was used to analyze factors related to disease-free survival. Potential factors related to disease-free survival were analyzed along with recurrence-to-operation interval divided by 1, 2 or 3 months.

All statistical analyses were performed using SPSS 20.0 (SPSS Inc., Chicago, IL). The Institutional Review Board of Samsung Medical Center approved this study (IRB No.2013-07-122).

Results

Demographic, surgical, clinical, and histological characteristics of the subject groups are summarized in Table 1. A total of 74 patients, 42 males (56.8%) and 32 females (43.2%), were included. Mean age was 55.3 years. Nearly two-thirds of patients were operated on after their first recurrence ($n = 51$, 68.9%). A total of 23 patients (31.1%) were operated on after multiple recurrences. Median interval between previous surgery and recurrence was 12.9 months (interquartile range 27.47). Median interval between recurrence and current operation was 1.68 months (interquartile range 3.77). Twenty-three patients (31.1%) were operated on within a month after recurrence. Twenty-two patients (29.7%) were operated on 1–2 months after recurrence. Seven patients (9.5%) were operated on 2–3 months after recurrence. Twenty-two patients (29.7%) were operated on more than 3 months after recurrence. The proportion of R2 resection in the salvage operation was 17.6% ($n = 13$). Thirty-four patients (45.9%) had multifocal recurrence. Mean tumor size was 16.7 cm, and 29.7%

Table 1 Demographical, histological, and clinical characteristics of patients who underwent salvage operation for recurrence of retroperitoneal liposarcoma

Factors	No. of patients	%
Sex, male/female	42/32	56.8/43.2
Mean age (years)	55.3 ± 11.4	
Disease status		
First recurrence	51	68.9
Multiple recurrence	23	31.1
Median interval between previous operation and recurrence (months, IQR)	12.9 (27.47)	
Median interval between recurrence and salvage operation (months, IQR)	1.68 (3.77)	
Within 1 month	23	31.1
1–2 months	22	29.7
2–3 months	7	9.5
After 3 months	22	29.7
R2 resection	13	17.6
Multiplicity		
Unifocal	40	54.1
Multifocal	34	45.9
Size (cm)		
Mean ± SD	16.7 ± 13.4	
0–5	5	6.8
5–10	27	36.5
10–15	10	13.5
15–20	10	13.5
More than 20	22	29.7
Adjacent organ invasion		
No invasion	42	56.8
Invasion	32	43.2
Differentiation of recurrent tumor		
Well-differentiated LPS	22	29.7
De-differentiated LPS	45	60.8
Myxoid/round cell LPS	3	4.1
Pleomorphic LPS	1	1.4
Others	3	4.1
FNCLCC Grade of recurrent tumor		
1	22	35.5
2	25	40.3
3	15	24.2
Undetermined	12	
Nephrectomy		
No nephrectomy	21	28.4
During previous operation	28	37.8
During salvage operation	24	32.4
Radiotherapy		
No radiotherapy	43	58.1
After previous operation	7	9.5
After salvage operation	24	32.4
Mean interval between operation and radiotherapy (months)	1.30 ± 0.29	
Mean duration of radiotherapy	1.22 ± 0.35	
Location of radiotherapy		
Retroperitoneum	27/31	87.1
Pelvis	4/31	12.9
Median number of fractions (n, IQR)	25 (4)	
Median dose (cGy, IQR)	5400 (750)	
Tissue expander insertion for radiotherapy	19/31	58.3
Recurrence after salvage operation	58	78.4
Death	45	60.8

Table 1 (continued)

SD standard deviation, *LPS* Liposarcoma, *FNCLCC* Fédération Nationale des Centres de Lutte Contre le Cancer

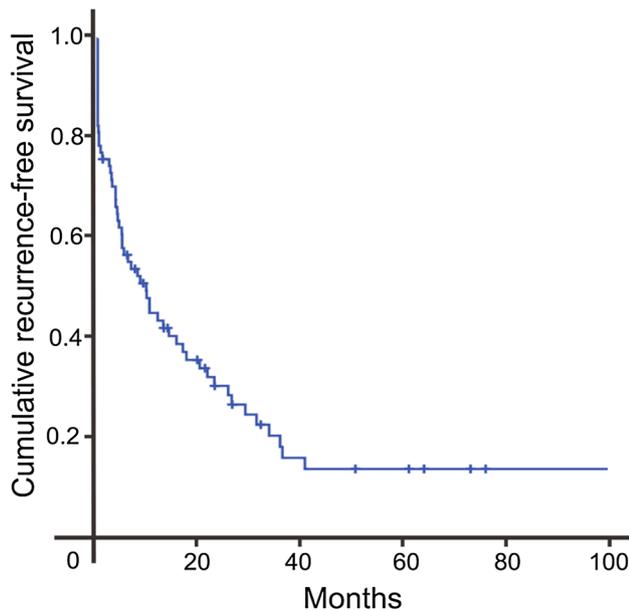


Fig. 1 Cumulative recurrence-free survival curves of patients who underwent salvage operation for recurrent retroperitoneal liposarcoma

($n=22$) of patients had a tumor larger than 20 cm. Twenty-two patients (29.7%) had well-differentiated liposarcoma (WDLPS), while 45 patients (60.8%) had de-differentiated liposarcoma (DDLPS). Recurrent tumor's FNCLCC grade 1, 2, and 3 were reported in 22 (35.5%), 25 (40.3%) and 15 (24.2%) patients, respectively. Twelve specimens were not classified with FNCLCC grade. While seven patients (9.5%) had RT after the previous operation as an adjuvant therapy, 24 patients (32.4%) underwent RT after salvage operation as an adjuvant therapy. There was no case with radiotherapy that was performed as an neoadjuvant therapy before operation. The mean interval between operation and radiotherapy was 1.30 ± 0.29 months and mean duration of radiotherapy was 1.22 ± 0.35 months. Forty-three patients (58.1%) did not have RT. Among 31 patients who underwent RT, 27 patients (87.1%) had RT on retroperitoneum while 4 patients (12.9%) had RT on pelvis. They had median number and doses of 25 (IQR 4) and 5400 cGy (IQR 750), and 19 patients (58.3%) were inserted with tissue expander for RT.

Recurrence occurred after salvage operation in 58 patients (78.4%). Death occurred in 45 patients (60.8%).

Prognostic factors for disease-free survival

Kaplan–Meier disease-free survival of patients is illustrated in Fig. 1. The 1-, 3-, and 5-year disease-free survival rates were 43.2%, 15.6% and 13.4%, respectively.

To analyze the prognostic relationship of recurrence-to-operation interval to disease-free survival, Cox analysis was performed with patients divided into two groups based on the time interval between prior recurrence and current operation. The time points for dividing patients were 1, 2 or 3 months.

Table 2 summarizes the results of multivariable Cox analysis including significant factors in univariable analysis. FNCLCC grade ($p=0.023$) and recurrence-to-operation interval of 3 months ($p=0.003$) were significant factors associated with recurrence. FNCLCC grade 2 showed a hazard ratio of 1.940 (CI 0.935–4.026, $p=0.238$) compared to grade 1, while grade 3 showed a hazard ratio of 4.049 (CI 1.767–9.281, $p=0.007$) compared to grade 1. Patients who underwent salvage operation more than 3 months after recurrence showed significantly increased risk of disease-free survival compared to patients who underwent salvage operation within 3 months after recurrence (HR 2.724, CI 1.391–5.337, $p=0.003$). Organ invasion (HR 1.223, CI 0.626–2.391, $p=0.641$) and radiotherapy ($p=0.176$) were only significant in univariable analysis. When patients were divided into two groups based on 1-month or 2-month recurrence-to-operation time intervals, univariable Cox analyses showed no significant relationship with disease-free survival. Figure 2 shows the disease-free survival curves of patients divided by two groups based on recurrence-to-operation interval of 3 months.

There was no difference between the FNCLCC grades between patients with recurrence-to-operation interval within 3 months and after 3 months. ($p=0.959$) In patients who underwent operation within 3 months, number of patients with grade 1, 2 and 3 were 17 (39.5%), 14 (32.6%), and 12 (27.9%), respectively. Number of patients with grade 1, 2 and 3 among patients who underwent operation after 3 months were 5 (26.3%), 11 (57.9%) and 3 (15.8%), respectively.

Discussion

Retroperitoneal LPS, one of the most invasive malignancies, that requires radical excision followed by extensive monitoring for potential remnant or recurrent tumor. For proper management, patients with retroperitoneal LPS should be managed in a high volume tertiary center

Table 2 Multivariable Cox proportional hazard ratio model of factors related to recurrence-free survival of recurrent retroperitoneal liposarcoma patients who underwent salvage operation

Factors	No.	Univariable			Multivariable		
		HR	95% CI	P	HR	95%CI	P
Sex				0.534			
Male	42						
Female	32	0.845	0.497–1.436				
Age (years) > 60	32	1.613	0.951–2.734	0.076			
Status				0.486			
First recurrence	51						
Multiple recurrence	23	1.217	0.700–2.116				
Recur-free duration of prior surgery				0.515			
Within 3 months	13						
More than 3 months	61	0.809	0.427–1.532				
Size \geq 10 cm	47	1.103	0.643–1.892	0.721			
Multiplicity	34	1.262	0.745–2.138	0.386			
Organ invasion	32	1.831	1.077–3.110	0.025	1.176	0.595–2.322	0.641
Combined organ resection	52	0.684	0.387–1.208	0.191			
Nephrectomy				0.060			
No nephrectomy	21						
During previous operation	28	1.031	0.546–1.945	0.926			
During salvage operation	24	0.496	0.249–0.988	0.046			
Histological margin				0.775			
Unknown	47						
Positive	27	1.082	0.629–1.863				
Differentiation				0.131			
WDPLS	22						
Other	49	1.587	0.872–2.889				
FNCLCC Grade				0.015			0.023
1	22						
2	25	2.117	1.038–4.318	0.039	1.940	0.935–4.026	0.238
3	15	3.148	1.430–6.927	0.004	4.049	1.767–9.281	0.007
Unknown	12						
Radiotherapy				0.036			0.176
No radiotherapy	43						
After previous operation	7	1.263	0.529–3.016	0.599	0.649	0.251–1.680	0.373
After salvage operation	24	0.470	0.252–0.878	0.018	0.539	0.276–1.054	0.071
Recur-to-operation interval				0.460			
Within 1 month	23						
More than 1 month	51	1.235	0.706–2.163				
Recur-to-operation interval				0.095			
Within 2 months	45						
More than 2 months	29	1.577	0.924–2.693				
Recur-to-operation interval				0.028			0.003
Within 3 months	52						
More than 3 months	22	1.869	1.068–3.271		2.724	1.391–5.337	

WDPLS well-differentiated liposarcoma, FNCLCC Fédération Nationale des Centres de Lutte Contre le Cancer

specialized in retroperitoneal STS. They should be cared for by a multidisciplinary team including surgical oncologists, medical oncologists, radiotherapists, pathologists, and radiologists.

Although retroperitoneal LPS is rare, prognostic factors related to its recurrence and death have been extensively studied and reported by high-volume centers around the world [7, 10–14]. Studies have investigated the pattern and

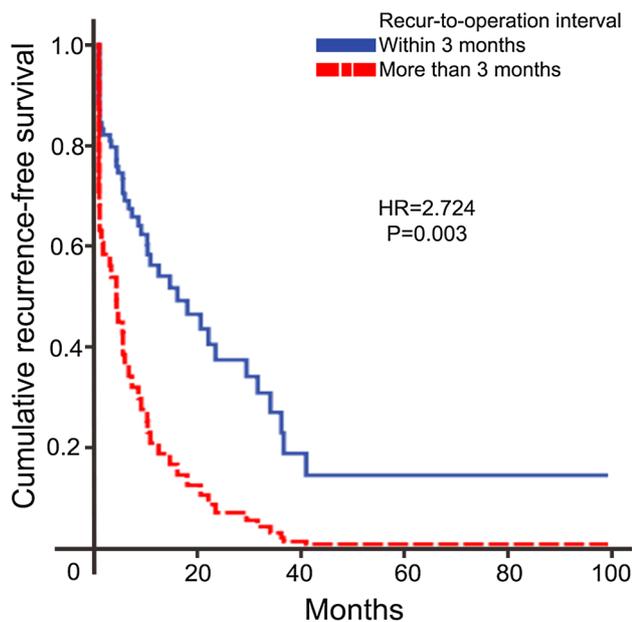


Fig. 2 Recurrence-free survival curves of patients categorized by recurrence-to-operation interval of 3 months showed that recurrence-free survival was significantly poorer in patients with recurrence-to-operation interval more than 3 months

findings of recurrence and prognosis. A study by Kim et al. described the characteristics of recurrent LPSs in an imaging study and showed that attenuation of recurrent LPS is similar to that of the primary tumor, which is slightly higher than that of normal retroperitoneal fat [16]. They also suggested a tumor volume doubling time of 93 days. Wang et al. published a study suggesting that long recurrence-free interval was related to favorable outcome after reoperation [17]. However, there have been no studies on how patients should be managed when there is an ambiguous finding suspicious for recurrent tumor.

Our center established a protocol for performing follow-up CT scans at 1 week, 3 months, and 6 months after operation. After 6 months, patients are followed up regularly for 3 months, until 2 years. After 2 years, patients are followed up for 6-month interval. If a patient underwent adjuvant RT, they eventually had additional CT scans for RT planning and follow-up. The protocol of frequent CT scans introduced the issue of how long can salvage operation be delayed when CT findings are suspicious but not diagnostic of recurrence. In many cases, early postoperative CT does not completely rule out remnant or recurrent tumor with normal postoperative change. When CT findings do not give complete evidence of recurrence, surgical oncologists often decide to observe patients with a short term CT follow-up. Sometimes, the suspected finding does not change for months or even for several years. However, it may be enlarged in the consecutive imaging study. Surgical oncologists also face a

dilemma whether to operate or follow-up a suspected recurrence, when it is too small. Abundantly, the surgeons fail to identify a small tumor, especially when the anatomy is obscure and the tumor's consistency is similar to normal fat. To minimize these difficulties, close monitoring of the tumor growth using short term CT follow-up can be used. This study was designed to find a maximum time limit for delaying salvage operation when tumor recurrence is suspected. Other than CT, magnetic resonance imaging (MRI) can be used as a diagnostic tool for retroperitoneal LPS. MRI can be especially useful for pediatric patients and myxoid/round cell LPS which can metastasize to the spine [18]. However, there are opinions that MRI is not suitable for distinguishing between benign and malignant tissue of LPS, but diffusion-weighted MRI can be used for overcoming the shortcoming [19, 20]. In our center, we performed CT as the primary imaging modality.

In our study, patients who underwent salvage operation more than 3 months since recurrence showed significantly poorer disease-free survival compared to patients who underwent salvage operation within 3 months since recurrence (HR 2.724, CI 1.391–5.337, $p=0.003$). Conversely, patients who had recurrence-to-operation intervals of more than 1 month (HR 1.235, CI 0.706–2.163, $p=0.460$) or 2 months (HR 1.577, CI 0.924–2.693, $p=0.095$) had no statistical differences in disease-free survival compared to patients who had recurrence-to-operation intervals of less than 1 month or 2 months, respectively. This result correlates with the finding by Kim et al. in which tumor volume doubling time was nearly 3 months [16].

It is obvious that recurrent tumors will progress without intervention. Nevertheless, deciding to operate for recurrent retroperitoneal LPS is complicated due to uncertainty on imaging and technical difficulty. The result that a recurrence-to-operation interval of more than 3 months has a negative impact on further recurrence may help oncologists plan treatment strategies for retroperitoneal LPS patients who are suspected to have recurrence on follow-up CT. When recurrence is not initially clear, additional follow-up CT scans can be obtained if they are obtained within 3 months to minimize the risk of progression. We recommend that a decision regarding suspected findings and surgical removal should be made within 3 months.

In our center, surgery was decided when recurrent mass was definite on follow-up CT. The situations that we considered definite for recurrence was an evident mass, or enlargement of a structure suspected to be a tumor recurrence during follow-up. We usually performed short term follow-up scans to minimize the risk.

This is a retrospective study with some limitations. Twenty-three patients (31.1%) had multiple recurrences before the current operation. Thirty-four patients (45.9%) had multifocal recurrent tumors from a prior recurrence.

Twenty-eight patients (37.8%) had nephrectomy in the previous operation while 24 patients (32.4%) had nephrectomy during the salvage operation for recurrence. RT was performed after the previous operation as an adjuvant therapy in seven patients (9.5%) while 24 patients (32.4%) had RT after the salvage operation for recurrence. Although these factors did not show significant relationships with recurrence-free survival, the included patients were heterogeneous. This study has an inherited limitation that it cannot represent the diverse clinical situations that clinicians face during their practice.

Furthermore, it is not appropriate to interpret that waiting less than 3 months has no additional risk on prognosis. It is more appropriate to conservatively interpret that when findings on CT are suspicious but not evident for recurrence, the patient should be closely observed for a maximum of less than 3 months if there are no other changes on consecutive CTs. On these occasions, we recommend frequent CT follow-up with 1 month intervals to minimize the risk to the patient. If there are signs of increased size, salvage operation should be strongly considered to avoid further delay from the initial recognition.

With these limitations, findings from our study require more evidence before creating guidelines for the clinical field. However, we believe that oncologists who work with retroperitoneal STS would agree that delayed surgical exploration is often chosen when ambiguous findings are seen on CT scan. This study focuses on how long can patients bare the risk of having a potential recurrent malignancy. Our study suggests that a maximum duration of within 3 months is optimal. This finding is a crucial time limit for oncologists in the field, and we hope that other high volume centers analyze their patients with recurrence to set a more precise limit of optimal maximum duration.

Compliance with ethical standards

Conflict of interest This authors have no conflict of interest related to this study.

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