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Factors affecting retroperitoneal liposarcoma recurrence and survival

Murat Guner[a,*], Tayfun Kaya[a], Cengiz Aydin[a]

[a] *Republic of Turkey Ministry of Health, University of Health Sciences, Tepecik Training and Research Hospital, Department of General Surgery, Izmir, Türkiye*

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Abstract

Aim: Retroperitoneal liposarcoma is a soft tissue malignancy that is typically seen as large mass lesions found incidentally on imaging. This study aimed to examine patients in light of clinicopathologic data and to investigate the reasons affecting recurrence and survival.

Materials and Methods: A total of 32 patients with pathologically proven primary retroperitoneal liposarcoma who were treated between January 2011 and December 2021 were analyzed.

Results: Thirty-two patients underwent surgery and all were treated with R0 resection. Recurrence was experienced by 12 (37.5%) patients and a further nine (28%) died during follow-up. The pathologic subtype of the tumor and the presence of fragmented specimens were found to be statistically significant with recurrence. Mortality was found to be high with 50% in patients with recurrence (p=0.049).

Conclusion: Fragmented resection of retroperitoneal liposarcoma specimens is related to recurrence. The pathologic subtype of the tumor is significantly related to recurrence and overall survival. Additional chemotherapy or radiotherapy had no significant effect on recurrence or overall survival.

Introduction

Liposarcomas (LPS) are malignant tumors of adipocytic differentiation and one of the most common histologies of soft tissue sarcoma, representing 50% of tumors in the retroperitoneal area [1]. This disease is classified into four main subtypes: well-differentiated LPS, myxoid LPS, pleomorphic LPS, and dedifferentiated LPS [2]. The histopathology of the disease significantly affects the course and prognosis of the disease.

There is a consensus in the sarcoma community that surgery to remove retroperitoneal LPSs with clear margins is the most beneficial treatment to improve recurrence-free survival (RFS) and OS. However, it is difficult in retroperitoneal LPS due to invasion to adjacent organs or vessels, and many patients thus develop recurrence. Most patients die of recurrences. Metastatic lymph node ratio was reported to be an ideal prognostic marker for stage III colon cancer patients in one study, but local recurrence and distant metastases affect the prognosis more significantly in patients with retroperitoneal liposarcoma [3]. The optimal treatment approach in patients with recurrence remains a controversial issue [4].

Herein, we examine the causes of recurrence and mortatity in patients who underwent surgery for retroperitoneal LPS and share our clinical experience in patients who developed recurrence.

Materials and Methods

A total of 32 retroperitoneal liposarcoma surgeries performed between January 2011 and December 2021 were evaluated retrospectively. All patients' ages, sex, tumor size and location, surgical procedures, and postoperative results with histologic diagnosis, margin status, receipt of chemotherapy or radiotherapy, recurrence, and mortality were evaluated retrospectively. Ethical approval was received from ethics committee of the University of Health Sciences Tepecik Training and Research Hospital (2020/13-37). All patients underwent preoperative imaging studies [computed tomography (CT) or magnetic resonance imaging (MRI)] to study the characteristics and size of the lesions. All patients were evaluated as radiologically operable. Retroperitoneal benign lesions and non-liposarcoma malignant lesions were excluded from the study. Patients who were aged under 18 years and who

*Corresponding author:
Email address: mgunerus@yahoo.com (Murat Guner)

had inadequate data were excluded from the study. Patients with R1 resections were excluded. Patients who were referred to our hospital for recurrence surgery were also excluded. All patients underwent open surgery and were treated with R0 resections. Frozen sections for surgical margins were studied in suspicious patients. Abdominal drainage was performed on all patients. For pathologic evaluations, liposarcoma was subclassified as well-differentiated, myxoid, pleomorphic, and dedifferentiated.

Satatistical analysis

The statistical analyses were performed using Statistical Package for Social Sciences version 2015. The categorical variables were presented as frequency and percent. The comparison between the groups in terms of distribution was performed using Pearson chi-square test. As the continuous variables were analyzed in terms of normal distribution through histogram, Q-Q plot, and Shaphiro-Wilk test, none of the variables were found to reveal normal distribution. Thus, throughout the text, the continuous variables were presented as median (minimum – maximum), the continuous variables between the two groups were compared using Mann-Whitney U test. A Kaplan-Meier survival analysis was performed using Log-rank (Cox-Mantel) test. A p value of less than and equal to 0.05 was considered statistically significant.

Results

After local ethics committee approval, the study was conducted at Izmir University of Health Sciences Tepecik Training and Research Hospital General Surgery Clinic between December 2011 and December 2021. A total of 32 patients who underwent surgery for retroperitoneal LPS were included in this retrospective cohort study. There were 13 women (40.6%) and 19 men (59.4%). The mean age was 55.5 years and the mean lesion size was 14.5 (7-32) cm.

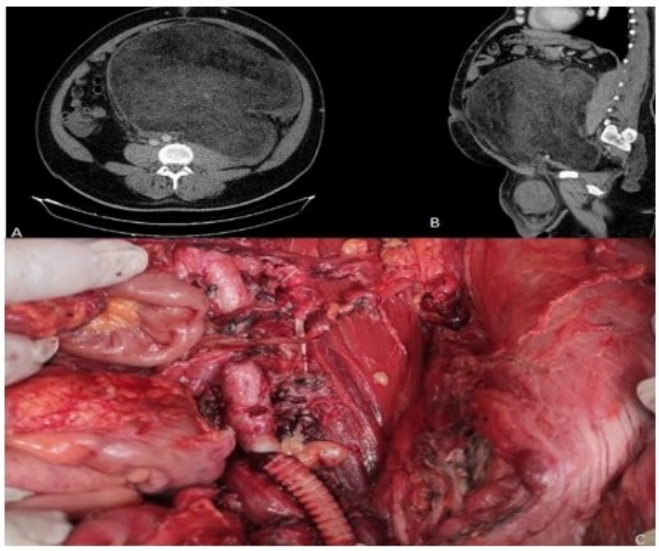

Figure 1. Patient CT image and operation side image. A: Coronal secton CT image of Retroperitoneal LPS, B: Axial section CT image Retroperitoneal LPS, C: Intraoperative image of patient after complete resection.

Table 1. Demographic and clinical characteristics of patients with and without recurrens with the research community.

Variables	Recurrence			
	Patients (n= 32)	Positive (n= 12)	Negative (n= 20)	p value
Age, year	55.5 (27 – 76)	54.5 (48 – 72)	56.5 (27 – 76)	0.954[a]
Gender				0.713[b]
Female	13 (40.6)	4 (33.3)	9 (45)	
Male	19 (59.4)	8 (66.7)	11 (55)	
Imaging methods				0.325[c]
CT	10 (31.3)	5 (41.7)	5 (25)	
MRI	22 (68.8)	7 (58.3)	15 (75)	
Tumor size, cm	14.5 (7 – 32)	17 (11 – 32)	13 (7 – 25)	0.076[a]
Tumor histopatology				**0.025**[c]
Well Differantiated	11 (34.4)	1 (8.3)	10 (50)	
Myoxoid LPS	15 (46.9)	7 (58.3)	8 (40)	
Pleomorphic LPS	3 (9.4)	3 (25)	0 (0)	
Dedifferantiated LPS	3 (9.4)	1 (8.3)	2 (10)	
Tumor resestion				**0.027**[b]
One piece	17 (53.1)	3 (25)	14 (70)	
Fragmented	15 (46.9)	9 (75)	6 (30)	
Margin				0.119[b]
Negativie	22 (68.8)	6 (50)	16 (80)	
Suspicious	10 (31.3)	6 (50)	4 (20)	
Resection of contiguous organs	8 (25)	3 (25)	5 (25)	1.0[b]
Chemotherapy	17 (53.1)	6 (50)	11 (55)	0.784[c]
Radiotherapy	10 (31.3)	2 (16.7)	8 (40)	0.248[b]
Mortality	9 (28.1)	6 (50)	3 (15)	**0.049**[b]

[a] Mann-Whitney U test, [b] Fisher's exact test, [c] Pearson's chi-square test.

The histopathology of patients was well-differentiated LPS in 11 patients (34.4%), myxoid LPS in 15 patients (46.9%), pleomorphic LPS in three (9.4%) patients, and dedifferentiated LPS in three (9.4%) patients.

In the pathology report of these patients, 22 had negative margins but 10 had suspicious margins. Seventeen patients had a single pathology specimen, and 15 patients had fragmented specimens. It was found statistically significant that more recurrences were seen in patients with muti-fragmented pathology specimens (p=0.027). The demographic characteristics of the patients are summarized in Table 1.

The numbers of surgeries were one in 22 patients, and two in 10 patients.

Eight patients needed organ resection in addition to li-

Table 2. Demographic and clinical characteristics of patients with and without mortality.

Variables	Mortality		
	Yes (n= 9)	No (n=23)	p value
Age, year	55 (51 – 72)	56 (27 – 76)	0.458[a]
Gender			0.249[b]
Female	2 (22.2)	11 (47.8)	
Male	7 (77.8)	12 (52.2)	
Imaging methods			1.0[b]
CT	3 (33.3)	7 (30.4)	
MRI	6 (66.7)	16 (69.6)	
Tumor size, cm	17 (11 – 32)	14 (7 – 30)	0.246[a]
Tumor histopatology			0.094[c]
Well Differantiated	1 (11.1)	10 (43.5)	
Myoxoid LPS	4 (44.4)	11 (47.8)	
Pleomorphic LPS	2 (22.2)	1(4.3)	
Dedifferantiated LPS	2 (22.2)	1(4.3)	
Tumor resestion			**0.049[b]**
One piece	2 (22.2)	15 (65.2)	
Fragmented	7 (77.8)	8 (34.8)	
Margin			1.0[b]
Negativie	6 (66.7)	16 (69.6)	
Suspicious	3 (33.3)	7 (30.4)	
Resection of contiguous organs	2 (22.2)	6 (26.1)	1.0[b]
Chemotherapy	5 (55.6)	12 (52.2)	1.0[b]
Radiotherapy	1 (11.1)	9 (39.1)	0.210[b]
Mortality	6 (66.7)	6 (26.1)	**0.049[b]**

[a] Mann-Whitney U test, [b]Fisher's exact test, [c] Pearson's chi-square test.

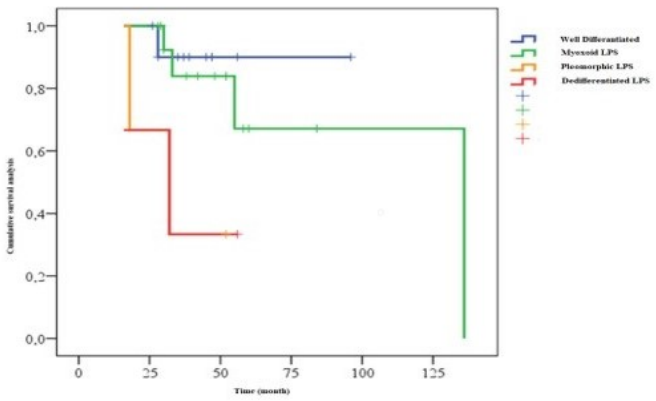

Figure 2. Survival analysis with tumor histopathology of patients. For the analyses of the patients' survival, the pleomorphic and liposarcoma group survival was significantly shorter compared to the well-differantiated and myoxoid LPS group [Log-rank (Mantel-Cox): X^2= 7.96, p=0.047]

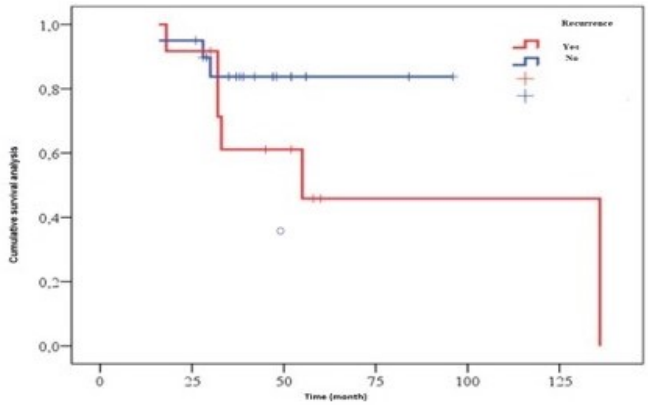

Figure 3. Recurrens and survival analysis of patients. Survival analysis seems to be better in non-recurred patients, but it was not statistically significant [Log-rank (Mantel-Cox): X^2= 1.81, p=0.178].

posarcoma resection; four patients had nephrectomies, three patients had colon resection, and one patient underwent sigmoid colon resection, left nephrectomy, internal and external iliac vascular resection, and reconstruction surgery for an en bloc resection (Figure 1). Three patients had wound infections, three patients needed a percutaneous drain for an intraabdominal abscess, and two patients had delayed postoperative ileus. None needed surgery for complications.

As an adjuvant treatment, chemotherapy was performed in 17 surgeries (53.1%) and radiotherapy was performed in 10 (31.3%) surgeries.

Twelve patients had a recurrence. Histopatology of the tumor was significantly related to recurrence (p=0.025). The quality of pathology specimens was also significantly related to recurrence. Nine of 15 patients who had fragmented specimens had recurrence (p=0.027). Ten of 12 patients with recurrence underwent a second surgery; however, no statistically significant results were found between the patients who had surgery a second time and those who were not reoperated (p=0.455). Ten patients had adjuvant chemotherapy and eight patients had radiotherapy after recurrence.

For the analyses of the patients' survival, the survival of the pleomorphic and dedifferentiated liposarcoma groups was significantly shorter compared with the well-differentiated and myxoid liposarcoma group [Log-rank (Mantel-Cox): χ^2=7.96, p=0.047] (Figure 2).

The median follow-up duration starting from the first surgery to the last follow-up was 40.5(range, 16-136) months. No patients died during the 30-day perioperative period. A total of nine (28.1%) patients died during their follow-up. Six of 12 patients (50%) with recurrence died. Demographic and clinical characteristics of patients with and without mortality are summarized in Table 2. For all patients, survival was 71.9% with a mean follow-up of 45.8 ± 23.8 days, and RFS was 62.5%. Survival analysis was better in patients without recurrence, but it was not

statistically significant [Log-rank (Mantel-Cox): χ^2=1.81, p=0.178] (Figure 3).

Discussion

LPS is the most common type of soft tissue sarcoma [5]. LPS is a frequently observed tumor originating from adipocytic differentiated primitive mesenchymal cells and it can occur anywhere in the body [6,7]. It is very difficult to determine retroperitoneal LPS and it is usually found incidentally. LPS peaks in the range of 40-60 years [8]. In the present study, the mean age at diagnosis was found as 55.7 years. There was no significant sex was observed difference in LPS occurrence, and the ratio of our patients was 19 (59.4%) males to 13 (40.6%) females.

Diagnosis of retroperitoneal LPS is often delayed by the absence of symptoms and due to their location; therefore, a tumor can reach a large size and invade neighboring organs at the time of diagnosis [9]. The sizes of the LPS tumors ranged from 7 to 32 cm in the present study, with a median diameter of 14.5 cm. No significant difference was observed between tumor size, recurrence, and OS. In the present study, 11 patients had well-differentiated LPS, 15 patients had myxoid LPS, three patients had pleomorphic LPS, and three patients had dedifferentiated LPS. Some studies reported that tumor histopathology is an independent predictor of OS in soft tissue sarcomas and analysis has shown that the histologic grade and pathologic subtype of tumors were independent prognostic markers [10-11]. In our study, it was found that tumor histopathology had a significant effect on survival, and this effect was prominent in pleomorphic and dedifferentiated LPS [Log-rank (Mantel-Cox): χ^2=7.96, p=0.047].

The pathology specimen is evidence of the quality of the surgical procedure and affects the prognosis of the disease. The current first-line treatment for LPS is negative margin surgical resection; positive margins are considered a prognostic factor for recurrence and OS. In their study of 152 patients, Nobre et al. reported that fragmented specimen removal in patients with uterine sarcoma was associated with higher recurrence rates [12]. It is very difficult to determine the margin in fragmented specimens. In this study, 22 patients had negative margins but 10 patients had suspicious margins. Seventeen patients had single pathology specimens, and 15 patients had fragmented specimens. In our study, fragmented specimens of tumor were found to be associated with recurrence (p=0.027), but when the effect on survival was evaluated, it was seen that survival was better in patients with en block or single-piece resection. No significant association was observed between pathology specimens and OS [Log-rank (Mantel-Cox): χ^2=3.27, p=0.070]. Removal of fragmented specimens may lead to disruption of tissue integrity, difficulties in the evaluation of surgical margins, possible positivity of surgical margins, and thus recurrence in a short time.

Other treatment modalities are used to improve retroperitoneal LPS prognoses, such as chemotherapy and radiotherapy, but there is no consensus on the effectiveness of chemotherapy or radiotherapy for retroperitoneal LPS. A multicenter study of 607 patients showed that perioperative radiotherapy was associated with better local control, but did not affect OS [13]. However, a recent randomized, phase 3 study performed with 266 patients, showed that the median RFS in the surgery plus radiotherapy group was 4.5 years compared with 5.0 years in the surgery alone group, suggesting that preoperative RT had no benefit [14]. In our study, adjuvant radiotherapy was performed on 10 patients with suspicious margins and radiotherapy had no significant effect on recurrence or OS.

The role of chemotherapy remains controversial in patients with retroperitoneal LPS. Some study reports are showing the significant efficacy of chemotherapy or neoadjuvant chemotherapy in retroperitoneal LPS; however, the supporting evidence for adjuvant chemotherapy in retroperitoneal LPS is unclear [15-16]. As an adjuvant treatment, chemotherapy was performed on 17 patients who had suspicious margins or pleomorphic LPS or dedifferentiated LPS. Chemotherapy had no significant impact on recurrence or OS in our patients.

Complete surgical resection with negative margins is the only curative therapy for patients with retroperitoneal LPS. In our study, organ resections were only performed in the presence of adjacent organ invasion during surgery. Eight patients needed organ resection in addition to liposarcoma; four patients had nephrectomies, three patients had colon resection, and one patient underwent sigmoid colon resection, left nephrectomy, internal and external iliac vascular resection, and reconstruction surgery for an en bloc resection. No statistically significant results were found between recurrence or OS in patients who underwent organ resection.

Abdominal recurrence is high even in high-volume centers; so many patients with retroperitoneal LPS develop a local recurrence and subsequently die without distant metastases [17]. In a study, OS in the early recurrence group was 42.7 months compared with 105.7 months in the group without early recurrence, and early recurrence had an impact on the reduction in OS. In addition, positive margins were associated with early recurrence [18]. In our study,12 patients had recurrence. Differentiation of the tumor is significantly related to recurrence (p=0.025). The quality of pathology specimens was also significantly related to recurrence; nine of 15 patients who had fragmented specimenshad recurrence (p=0.027). In a study, Park et al. found a local recurrence growth rate was >0.9 cm/month [19], but in this study, the mean time of recurrence was found as 21.5 (range, 14-63) months and the mean size of tumors was 12 (range, 5-18) cm (>0.56 cm/month). Ten of 12 patients with recurrence had a second surgery; however, no statistically significant results were found between the patients and OS of those who underwent surgery for the second time and those who did not (p=0.455). Survival analysis was better in patients without recurrence, but the difference was not statistically significant [Log-rank (Mantel-Cox): χ^2=1.81, p=0.178]. For all patients, survival was 71.9% with a mean follow-up of 45.8 ± 23.8 months, and RFS was 62.5%. Survival analysis was better in patients without recurrence, but the difference was not statistically significant [Log-rank (Mantel-Cox): χ^2=1.81, p=0.178].

This study has several limitations. First, as a retrospective study, initial medical records may have had missing data, recall bias, and errors. Second, the study population was

relatively small. Third, there was no standard surgical procedure or algorithm for the treatment of patients with recurrence.

Conclusion

In conclusion, fragmented tumor specimens were found to be associated with recurrence; however, our analyses showed that the histopathologic subtype was more likely to determine survival than recurrence in patients with retroperitoneal LPS.

Ethical approval

Ethical approval was received from ethics committee of the University of Health Sciences Tepecik Training and Research Hospital (2020/13-37).

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