Joint Diseases and Related Surgery

ORIGINAL ARTICLE

Evaluation of prognostic factors and oncological outcomes in patients with limb-localized myxoid liposarcoma

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Liposarcoma (LPS) is the most commonly seen soft tissue sarcoma (STS) in the extremities in adults. According to the 2013 World Health Organization (WHO) classification, there are five subtypes of atypical lipomatous tumor/well differentiated, de-differentiated, myxoid/round cell, pleomorphic, and other unidentified types.[1] Liposarcomas are a heterogenous tumor group with clinically different histopathological characteristics in respect of histological appearance and biological behavior. For instance, while atypical lipomatous type has a good prognosis without metastatic potential, high-grade myxoid and pleomorphic LPS subtypes have a poor prognosis and high metastatic cycle.

Although peak incidence is in the fourth to fifth decades, myxoid liposarcomas (MLS) is the most common LPS subtype in children and adolescents.

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ABSTRACT

Objectives: This study aims to evaluate the prognostic factors and treatment outcomes of patients with extremity-localized myxoid liposarcoma (MLS).

Patients and methods: Between January 2001 and October 2019, a total of 43 patients (29 males, 14 females; mean age: 56.3±11.4 years; range, 34 to 76 years) who were histopathologically diagnosed with MLS in our clinic were retrospectively analyzed. Data including demographic characteristics, tumor localization, tumor volume and length, histopathological characteristics, the surgery and chemotherapy (CT)/radiotherapy (RT) applied, survival rates, and complications such as local recurrence and metastasis were recorded. The treatment results and potential prognostic factors were identified. The overall survival (OS) and cancer-specific survival (CSS) rates were evaluated.

Results: The mean follow-up was 106.8±54.1 (range, 29 to 204) months. The mean tumor size was 11.4±6.5 (range, 4.7 to 36) cm. Tumor localization was determined as lower extremity in 76.7% of cases and upper extremity in 23.2%. The patients were divided into two groups according to the type of RT they received as follows: the patients who underwent neoadjuvant RT + wide surgical resection (n=14, 32.5%) and patients who underwent extensive surgical resection + adjuvant RT (n=29, 67.4%). To four patients who developed distant metastasis and to two who developed local recurrence, adjuvant CT was applied. In the whole cohort, the OS rate was 87.1% at five years and 73.2% at 10 years. The five and 10-year CSS rates were 83.5% and 66.4%, respectively. Local recurrence developed in 12 (27.9%) and distant metastasis in four (9%) patients. In the multivariate analysis, high tumor grade, R2 margins, and metastasis were found to be independent risk factors for OS. Although wide resection provided significantly good local control, neoadjuvant RT and adjuvant CT were not found to be prognostic factors for OS or CSS (p>0.05).

Conclusion: High tumor grade, R2 margins, and metastasis are independent risk factors for increased OS and OSS. Surgery with CT and neo/adjuvant RT is not an independent risk factor for OS or CSS. Despite patients with a larger tumor size and neurovascular proximity, similar disease-free survival rates can be achieved in the patients receiving neoadjuvant RT. Neoadjuvant RT can be considered in lesions close to neurovascular structures or in large lesions, with a high risk of wound complications.

Keywords: Extremity, myxoid liposarcoma, prognostic factors, radiotherapy.

Myxoid liposarcomas are typically localized in the deep soft tissues of the extremities, most often the thigh.[2]

Surgical resection is the main treatment modality in MLS, as well as in moderate and high-grade STS. Radiotherapy (RT) also plays an important role in the treatment of limb MLS. It has been reported that MLS is relatively sensitive to RT and chemotherapy (CT), compared to STS types.[3,4] Myxoid liposarcoma constitute 15 to 20% of all LPS and are the second most common type of LPS.[4] Radiotherapy can be used both preoperatively and postoperatively.[5] However, the choice between using RT preoperatively or postoperatively in MLS is still debated.[3,6]

A combination of surgery and adjuvant RT is used to improve local control of the disease and reduce recurrences. However, the use of neoadjuvant RT has gained popularity, as it can provide potential tumor shrinkage, better local control, and the need for lower adjuvant RT doses to reduce the complication rate.[7]

In the literature, there are several studies examining the prognostic factors and treatment modalities of patients with extremity MLS, mostly on a single-center, small-medium scale.[8-13] Surgical resection remains the first-line treatment for MLS. However, due to its high radiosensitivity, neo- or adjuvant RT can be used in therapy. Comparative studies are needed for optimal treatment management of MLS.

In the present study, the primary objective was to investigate potential prognostic factors by demonstrating long-term oncological outcomes in our series of patients with MLS. The second objective was to investigate the effect of neoadjuvant RT and adjuvant RT applied in the treatment of the disease on local recurrence (LR) and survival.

PATIENTS AND METHODS

This single-center, retrospective study was conducted at Ondokuz Mayıs University Faculty of Medicine, Department of Orthopedics and Traumatology between January 2001 and October 2019. Among a total of 218 patients diagnosed with LPS, 43 patients (29 males, 14 females; mean age: 56.3±11.4 years; range, 34 to 76 years) diagnosed with MLS were included. The clinical data of all the adult patients treated in our clinic for STS were retrieved from the hospital database. All the MLS subtypes were included in the study, primarily "pure MLS" or "myxoid/round cell liposarcoma (MRCLS)". The data obtained included demographic characteristics,

tumor localization, tumor volume and length, histopathological characteristics, surgery applied to patients, surgical margin status, neoadjuvant treatments such as CT-RT, survival rates, and complications such as LR and metastasis.

Biopsy was performed to the patients following magnetic resonance imaging (MRI) evaluation, and five of the study patients were referred to our center from an external center based on the biopsy result. After diagnosis, treatment planning was tailored by the Multidisciplinary Tumor Council. The surgical treatment of all patients in this study was applied by a single surgeon who was experienced in adult sarcoma.

Tumor grading in primary and recurrent cases were graded according to the 2013 WHO classification of STSs. Initial staging included physical examination and MRI of the lesion, unless contraindicated, and the lungs were evaluated by plain chest X-ray or computed tomography. Metastasis status was investigated in symptomatic patients after treatment using MRI or whole-body MRI and chest and abdominal computed tomography, depending on the clinician's preference. Surgical resections were defined according to the "R" classification of the International Cancer Control Association (ICCA).

Neo/adjuvant RT combined with surgical resection was administered to all adult (≥18 years) patients with biopsy-proven MLS that was not metastatic in the extremity. Treatment management was planned by the Multidisciplinary Team specialized in tumor surgery. There was a total dose of 45 to 50 Gy and 60 Gy in the pre- and postoperative period, respectively. While wide resection + neo/adjuvant RT was applied in cases of metastasis and recurrent LR, these patients were given doxorubicin + ifosfamide protocol as adjuvant CT.

Data including demographic characteristics, tumor size, tumor stage, surgical treatment, RT and CT protocols given, cause of death, and survival time were analyzed using the hospital data system. Adult (≥18 years old) with biopsy-proven MLS in the extremity without metastatic disease patients were included in the study. Patients were excluded from the study, if they did not accept the treatment to be applied after diagnosis, if the follow-up period was shorter than two years or they did not attend to follow-up appointments regularly, if they withdrew from treatment before completion, or if there were insufficient data in the files. In the light of the data obtained, the treatment outcomes and potential prognostic factors were analyzed.

Statistical analysis

Statistical analysis was performed using the IBM SPSS version 25.0 software (IBM Corp., Armonk, NY, USA). Descriptive data were expressed in mean ± standard deviation (SD), median (min-max) or number and frequency, where applicable. Both overall survival (OS) and cancer-specific survival (CSS) were evaluated using the Kaplan-Meier method. Univariate/multivariate analyses were performed with the log-rank test. A p value of <0.05 was considered statistically significant.

RESULTS

The mean follow-up was 106.8±54.1 (range, 29 to 204) months. The patients were divided into two groups as adult (<60 years) and older adult (≥60 years). Age and sex did not have any significant effect on OS (p<0.05). According to the tumor localization, the patients were divided into two groups as upper extremity and lower extremity. Tumor localization was determined as lower extremity in 76.7% of cases and upper extremity in 23.2%. Upper extremity localization was associated with low OS and CSS rates, indicating no statistically significant difference (p>0.05). Considering the proximity of the tumors to neurovascular structures, it was adjacent to the sciatic nerve (n=4), brachial artery (n=3), popliteal artery (n=3), femoral artery (n=2), and the brachial plexus (n=1).

In the pathological evaluation, the mean tumor size was found to be 11.4±6.5 (range, 4.7 to 36) cm. The patients were divided into three groups according to the tumor size as 0-5 cm, 5-10 cm, and ≥10 cm. Patients with a tumor size of ≥10 cm were shown to be associated with lower survival (p=0.045) and a higher possibility of recurrence (p=0.076). Tumor grade was determined as low grade in 16 patients and high grade in 27 patients. The 10-year OS rates were 86.3% in low-grade patients and 46.2% in high-grade patients (p=0.022). When the cases were classified according to the rate of round cells (RCs), 23 were determined with <5% RC, 12 with ≥5% RC and, in eight, there were pure myxoid cells with 0% RC. In the ≥5% RC group, the rate of OS decreased dramatically from 91.7% at two years to 50% at 10 years and it was found to be an independent risk factor for decreased OS (p=0.041). The resection margins were determined as R0 in 18 patients, R1 in 17, and R2 in eight, with 10-year OS rates of 94.4%, 65.5%, and 33%, respectively (p=0.024). High tumor grade, ≥5% RC, R2 resection margins, and LR were observed to have a statistically significant negative effect on OS and CSS (p<0.05). The demographic and

clinical characteristics of the patients are presented in Table I.

In the whole cohort the OS rate was 93% at two years, 81.2% at five years, and 72.7% at 10 years. The two and five-year CSS rates were found to be 88.4% and 71.5%, respectively. Mortality developed in seven patients because of tumoral disease and in four patients because of cardiovascular or renal pathologies, and thus at the final follow-up, 32 (74.4%)

TABLE I			
Patient and disease characteristics			
	n	%	Mean±SD
Age (year)			56.3±11.4
<60	28	65.1	
≥60	15	34.8	
Sex			
Male	29	67.5	
Female	14	32.5	
Location			
Upper limb	10	23.2	
Lower limb	33	76.7	
Tumor size (cm)			11.4±6.5
<5	8	18.6	
5-10	18	41.9	
≥10	17	39.5	
Tumor grade			
Low grade	16	37.2	
High grade	27	62.7	
Round cells (%)			
0 (Pure myxoid)	8	18.6	
0-5	23	53.5	
≥5	12	27.9	
Surgical margin			
R0	18	41.9	
R1	17	39.5	
R2	8	18.6	
Local recurrence			
Yes	12	27.9	
No	31	72.1	
Metastasis			
Yes	4	9.3	
No	39	90.6	
Surgery with RT			
Adjuvant RT	29	67.4	
Neoadjuvant RT	14	32.5	
Chemotherapy			
Yes	4	9.3	
No	39	90.6	

RT: Radiotherapy.

patients were alive. Wound necrosis developed in six patients during follow-up. The OS and disease-free survival (DFS) rates are shown in Table II.

In the primary treatment of the tumor, 14 (32.5%) patients underwent neoadjuvant RT + wide surgical resection, and 29 (67.4%) patients underwent wide surgical resection + adjuvant RT. Although the five-year OS rates were worse in the neoadjuvant RT + wide resection group (74.7%) than in the patients who underwent resection + adjuvant RT (80%), there was no significant difference in OS (p=0.349). The neoadjuvant RT group achieved a similar 10-year DFS rate (70.8% *vs.* 73.3%) despite the mean tumor size of the other group (11±5.3 cm *vs.* 13.3±8.5 cm) (p=0.691). Although the group with <5% RC had a lower risk of LR after neoadjuvant RT (p>0.05), there was no overall significant effect (p>0.05). However, the neoadjuvant RT group had a higher rate of wound complications compared to the other group (6.8% compared to 21.4%).

	Survival rate at 5 years		Survival rate at 10 years		Overall survival	DFS rate at 5 years		DFS rate at 10 years		DFS
Categories	n	%	n	%	*p*	n	%	n	%	*p*
Age (years)					0.283					0.146
<60	91.1		79.7			64.0		42.7		
≥60	78.8		52.5			90.9		65.3		
Sex					0.519					0.402
Male	82.8		74.4			68.5		68.5		
Female	78.6		69.8			77.9		77.9		
Location					0.314					0.451
Upper limb	78.8		56.3			78.8		78.8		
Lower limb	81.8		78.1			69.3		69.3		
Tumor size (cm)					0.045					0.076
<5	87.5		87.5			87.5		87.5		
5-10	94.4		88.9			83.3		83.3		
≥10	70.1		49.6			57.8		51.3		
Tumor grade					0.022					0.036
Low grade	90.0		86.3			83.1		83.1		
High grade	61.5		46.2			53.8		44.9		
Round cells (%)					0.041					0.377
0 (Pure myxoid)	100		100			87.5		87.5		
0-5	87.0		75.3			73.9		73.9		
≥5	58.3		50.0			55.6		55.6		
Surgical margin					0.024					0.086
R0	94.4		94.4			88.9		88.9		
R1	82.4		65.5			63.7		63.7		
R2	50.0		33.3			50.0		50.0		
Local recurrence					0.029					
Yes	58.3		48.6			71.5				
No	93.5		82.0			95.5				
Metastasis					0.011					0.01
Yes	0		0			0		0		
No	89.5		80.1			81.9		81.9		
Surgery with					0.249					0.391
Adjuvant RT	85.9		78.1			77.9		75.2		
Neoadjuvant RT	71.4		51.9			64.3		60.0		

TABLE II — Overall and disease-free survival rates

DFS: Disease-free survival; RT: Radiotherapy.

TABLE III			
Hazards ratio estimates with 95% CI and *p* values from the Cox proportional hazards model on 10-year overall survival			
Categories	HR	95% CI	*p*
Tumor size (cm)			0.405
<5	0.3	0.2-4.5	
5-10	0.98	0.8-11.1	
≥10	Reference	Reference	
Tumor grade			0.049
Low grade	1.6	1.2-5.9	
High grade	Reference	Reference	
Surgical margin			0.047
R0	Reference	Reference	
R1	1.6	0.48-73.3	
R2	9.8	5.6-106.2	
Local recurrence			0.279
Yes	1.1	0.1-7.3	
No	Reference	Reference	
Metastasis			0.034
Yes	16.3	1.2-215	
No	Reference	Reference	
CI: Confidence interval.			

Local recurrence developed in 12 (27.9%) patients following primary treatment, and all of these were in the region previously exposed to radiation. The mean time from primary treatment to the development of relapse was 1.9±0.8 (range, 1.3 to 5.2) years. Local recurrence had a significant effect on CSS and OS compared to patients without LR (p=0.029). Following the first LR, wide surgical resection + adjuvant RT or amputation surgery was performed. In the follow-up period after treatment for the first LR, a second recurrence was observed in five (15%) patients, for which the same protocol was applied again. In one of these patients, a third LR was determined after 63 months and transtibial amputation was performed following adjuvant CT. The 10-year OS multivariate analysis of the relevant factors is given in Table III.

Distant metastases were three soft tissue (lung/retroperitoneal) and one pelvis metastasis. These cases who developed distant metastasis were treated with wide surgical resection+ neo- and adjuvant RT with additional adjuvant CT. Including all patients who developed distant metastases, 51.4% of those who developed LR after the primary treatment were lost during follow-up. The development of metastasis and LR was a negative prognostic factor (p<0.01).

DISCUSSION

Liposarcoma are one of the sarcoma types that occur in adults characterized by adipocyte differentiation. The clinical behavior of LPS usually shows a close relationship to histopathological characteristics.[14] Several studies in the literature investigating the character of extremity MLS, prognostic factors, and appropriate treatment methods are often small- to medium-scale reports.[8-13]

Myxoid liposarcoma is usually diagnosed in adults and is rarely seen in children. In one previous report in the literature, age >60 years and, in another report, age >30 years were shown to be an independent predictor of generally worse and DFS of extremity MLS.[10,12] In the current study, although 34.8% of the patients were aged ≥60 years, the age factor did not have any effect on either OS or CSS (p>0.05). Moreover, according to sex, there was no significant difference in the survival rates. There are also reports in the literature that sex is not an independent negative prognostic factor in respect of survival.[15] According to tumor localization, despite the relationship in the current study between a worse outcome of cases with lower extremity involvement, this was not found to be an independent prognostic factor for reduced OS (p>0.05). In this respect, the results of the current study are consistent with the findings of previous reports.[9]

Tumor size is widely accepted as a prognostic factor for STS. In the current study, increased mortality was observed, when the tumor size was ≥10 cm (p<0.05). On the other hand, in our study, although it was found to be significant in terms of survival in the univariate analysis in the patient group with a tumor length of >10 cm, it lost its effect on survival in the multivariate analysis. Although an association of tumors >10 cm or >15 cm with poor prognosis has been reported in various studies in the literature, there are also studies reporting no relationship between the tumor size and survival.[10,13,16]

According to the complications in the current study, the mean tumor size was found to be 13.5±6.6 cm in the 12 patients with LR and 9.2±6.4 cm in patients without LR (p<0.05). The mean tumor size was 12.7±6.6 cm in the four patients with distant metastasis and 10.3±2.3 cm in patients without metastasis (p>0.05). As a large tumor size probably increases the possibility of proximity to neurovascular structures, it could be thought to be associated with poor prognosis and low survival

rates by increasing the probability of local recurrence and metastasis.

There are several reports in the literature showing that histological grade and RC percentage are prognostic factors affecting OS.[14,17,18] Muratori et al.[9] reported that tumor grade was an important risk factor affecting OS of MLS, while Wu et al.[10] reported that tumor grade was an independent prognostic factor for both OS and CSS. In the current study, the 10-year OS rates were 86.3% in low-grade patients and 46.2% in high-grade patients (p<0.05). In a previous study, the five-year OS rates for low-grade and high-grade patients were reported to be 92% and 74%, respectively.[18]

Another histological parameter evaluated in the current study was the RC percentage. The OS rates in the <5% RC group were 87.0% at five years and 75% at 10 years, while in the ≥5% RC group, they were 58.3% and 50%, respectively (p<0.05). In the study of Haniball et al.,[14] the five-year OS rate was 91% for pure MLS patients and 88% for those with <5% RC, and significantly worse at 58% for MLS patients with ≥5% RC. In contrast, Fiore et al.[11] reported a five-year survival rate of 87% for a group with ≥5% RC. This could be due to differences in the patient selection, treatment protocol (addition of CT), or pathological evaluation in the Fiore et al.'s study.[11] Haniball et al.[14] showed that the presence of >5% RC significantly increased the risk of LR by 5.9-folds. Similarly, Lemeur et al.[17] reported that if the tumor contained >5% RC, there was a 3.86-fold greater risk of LR. In the current study, this rate was found to be 1.9-fold. However, LR development had a significant impact on OS, with the five-year survival rates of 58.3% and 93.5% in those with and without LR, respectively (p=0.029). These results are consistent with previous findings in the literature.[19,20]

Metastatic disease is known to have a strong effect on survival with poor outcomes.[21,22] Although the metastasis rate was low in the current series, the patient group with distant metastasis developing during the disease course had a median survival of 34 months and all of these patients were lost during follow-up (p<0.05). Local recurrences were found to increase the risk of developing metastases (p=0.04) and local recurrence and metastatic event were found to be an independent prognostic factor with a significant effect on OS (p<0.01). However, the low metastasis rate may be a reflection of the relatively low number of patients with high-grade disease in the MLS cohort and resection with a safe surgical margin.

There are several studies in the literature showing that survival rates are better in LPS patients applied with wide resection and the margin is an important factor affecting survival.[11,14,23] In our study, the effect of surgical margin on OSS was significant (p=0.024), but its effect on CSS was not statistically significant (p=0.086). Similar to our study, Muratori et al.[9] showed that surgical margins had an impact on OS, while local recurrence-free survival (LRFS) was not correlated with the margins.

In a series of 418 MLS patients, Moreau et al.[8] reported that five-year LRFS rates were 95% for negative margins, 83% for R1, and 43% for R2 (p<0.01). In our study, CSS rates were found to be 88.9%, 63.7%, and 50%, respectively (p=0.08). In addition, the risk of LR development was 3.1-fold greater in patients with positive surgical margins (R1+R2) compared to patients with R0. On the other hand, although the LR rate in patients who underwent wide resection was approximately the same as those who underwent marginal resection, there was no significant difference in the survival analysis (p>0.05). Zheng et al.[24] reported that although wide resection could provide better local control than marginal resection, there was no significant difference in terms of long-term survival.

The combination of surgery and neo- or adjuvant RT in the treatment of extremity MLS is thought to improve local control of the disease and play an important role in reducing recurrence.[22,25] Fiore et al.[11] compared the patient groups who underwent surgery alone and surgery + adjuvant RT. In the multivariate analysis, postoperative RT was associated with a lower rate of LR and the risk of developing LR was reduced by approximately 50% (p<0.05). ten Heuvel et al.[26] also found a significant reduction in LR, when its adjuvant was combined with RT (44% *vs.* 8%; p<0.05). Since we did not have a control group that did not receive RT, no comparison could be made in terms of LR and survival. However, groups with and without surgical resection + adjuvant RT and neoadjuvant RT + resection were compared, and there was no significant effect of treatment types on LR.

There seems to be an increase in the number of recent studies in the literature reporting that there may be an effect on survival and LR with the application of neoadjuvant RT combined with surgery in the treatment of LPS.[7,16,27] However, most large-scale studies comparing pre- and postoperative RT still include all STS subtypes, not just MLS.[6,28,29] In the study of Lazarev et al.,[6] postoperative RT did not find a superior benefit in terms of survival

and LR compared to preoperative RT, while Koseła-Paterczyk et al.[30] reported that neoadjuvant RT was a viable method providing good local control and low treatment toxicity rates. Salduz et al.[16] also reported that neoadjuvant RT had an effect on the histopathological level, but despite the treatment, it did not affect the oncological outcomes of patients in respect of LR and metastasis.

In the current study, OS and CSS rates were slightly worse in the neoadjuvant RT group compared to the adjuvant group and, as a result, neoadjuvant RT had no effect on survival or prevention of LR. We were unable to find any factor affecting survival in the patient groups given neoadjuvant RT in terms of high grade, surgical margin, or localization. Although there were patients with larger volume and close to vascular nerve structures in the neoadjuvant RT + resection group, OS and CSS rates were close in both treatment types; therefore, neoadjuvant RT + resection may suggest that the treatment modality is relatively reasonable.[31]

However, the timing of use of RT in treatment is multifactorial and it should be evaluated on a case-by-case basis. However, the use of neo- or adjuvant RT in the treatment of MLS still remains unclear due to the lack of high-quality evidence addressing comparative studies.

It has been well documented that MLS is a chemosensitive tumor. Therefore, neo- or adjuvant CT may be recommended in cases such as large volumes or metastases.[4,32] In the current study, adjuvant CT of doxorubicin and ifosfamide was administered to four due to metastatic disease. All of these patients developed mortality due to disease progression. This result does not negate the efficacy of CT, as these patients with a large tumor volume who developed LR were not selected randomly.

Nonetheless, there are some limitations to this study. First, it has a retrospective design with a relatively small sample size. Second, that surgical treatment combined with CT and RT was used in selected patients which limits the statistical analysis of the study data of adjuvant treatment. The third limitation is that the study only examined the pathological subtype of MLS and tumor localization was restricted to the extremities. All these limitations may have resulted in deficiencies in the LPS analyses and a definitive prognosis may not be obtained in clinical practice.

In conclusion, in patients with extremity MLS, high grade, R2 margin, and metastases are independent risk factors for increased OS and CSS. Surgery with

CT and neo/adjuvant RT is not an independent risk factor for OS or CSS. Despite patients with a larger tumor size and neurovascular proximity, similar DFS rates can be achieved in the patients receiving neoadjuvant RT. Neoadjuvant RT can be considered in lesions close to neurovascular structures or in large lesions, with a high risk of wound complications.

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