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Management and Prognostic factors of survival liposarcoma of the limbs: A retrospective study of 50 patients.

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Abstract:
Background*:*
The purpose of our study was to analyze epidemiological, clinical and therapeutic data to determine histoprognostic risk factors associated with overall survival (OS) and progression free survival (PFS) in the liposarcoma (LS) of the limbs.
Methods:
This was a retrospective study of 50 cases ofLS of the limbs treated at the Salah Azaiz institute from 1995 to 2015. We analyzed the clinical, pathological features and outcome of our patients.
Results:
By the histological subtype, 5 years OS was 82% in well differentiated, 61% in myxoid, 50% in mixed and 0% in pleomorphic and dedifferentiated (p=0.002). The 5 years OS was 81% and 60% for grade 1, and 10% for grade 3 (p<0.001). Radiotherapy increased the OS from 40% to 70% at 5 years and from 29% to 43 at 10 years (p=0.063). The 2 and 5 years DFS were 36% and 19%, respectively. The one year DFS was 35% for patients with tumors ≤10cm and 0% for tumors >10cm (p=0.013). The one year DFS was 36% for pleomorphic and 0% for myxoid and dedifferentiated (p=0.005). The high grade decreased significantly the 2 years DFS from 37% in case of grade1 to 0% for the grade 3 (p<0.001). Involved surgical margins decreased the one year DFS from 10% to 0% (p<0.001). High grade (p=0.036) and involved margins (p=0.005)werethe independent predictive factors of metastases.
Conclusions:
Complete surgical resection remains the only curative treatment of LS, radiotherapy and chemotherapy could be useful especially for prevention and treatment of the relapses.
Keys words: *Limbs, liposarcoma, outcome, treatment*

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I. Introduction

The soft tissue sarcomas (STS) are rare tumors that regroup more than 80 histological entities(1). Liposarcoma (LS) is the most common histological type of STS (20-30%) (1,2). These tumors arise from the connective tissues (4).Cytogenetics and molecular biology have clearly distinguished different subtypes of LS, this distinction is important in terms of the natural history of these tumors and their diagnostic and therapeutic management (3). As publications on liposarcomas are rare, the identification of prognostic factors and optimal treatment remain insufficient.

II. Methods

We report a retrospective study including 50 patients treated for liposarcoma of the limbs at the Salah Azaiz institute from 1995 to 2015. The others sites of liposarcomas and cases with incomplete histology were excluded.

We collected clinical data (age, gender and physical examination) histological tumor features and outcome (the median follow up and the delay of relapse). All cases of LS were diagnosed by surgical biopsies and classified into histological subtypes according to the World Health Organization(WHO) classification (2002)(3). The grade was reported According to FNCLCC grading system(4). Patient's consent were obtained prior to any surgical procedure or irradiation or administration of chemotherapy. Limb salvage surgery was performed in all cases of localized tumor. In case of involved margins, we indicated a wide re-excision or

amputation. Radiotherapy was indicated if the tumor size exceeded 5 cm, deep to the fascia, high grade LS, close margins and locoregional relapses. We administrate 60 GY with a boost in the 4 to 10 GY in the tumor bed in the case of close margins or high grade LS due to the high risk of relapses. Different protocols of chemotherapy (CT) were administrated including Anthracycline Agents. Neoadjuvant chemotherapy was indicated for locally advanced tumors. Adjuvant CT was administrated for tumors with high risk of relapse (high grade, involved margins or relapse). Palliative CT was indicated for metastatic disease.

The main objective of our study was to analyze epidemiological, clinical and therapeutic data to determine the prognostic factors associated with overall survival (OS) and progression free survival (PFS).

The statistical analysis was performed with the SPSS 20 software. We defined the OS as the delay between the date of the histological diagnostic and the date of death. PFS was defined as the delay between surgery and locoregional or distant relapse of tumor process during or after the end of treatment. The survival curves were established by Kaplan-Meir methods and correlated with the prognostic factors using the Log Rank test. Multivariate logistic regression included clinical, histoprognostic tumor characteristics and therapeutic protocols to identify the independent predictive factors of metastases. The value $p < 0.05$ was considered statistically significant.

III. Results

Between 1995 and 2015, a total of 50 cases of LS of limbs were treated in our institute with frequency of 2.5cas / year and a sex ratio=0.78 (44% men and 56% women). The mean age was 50 years [range,22-90]. Isolated painless swelling was the main presenting symptom (n=49, 98%). Proximal location of the tumor was found in 89% of tumors of lower limbs and in 66% of tumors of the upper limbs. The mean tumor size was 14 cm [range, 3-40]. All patient underwent surgical biopsy for histological confirmation. The distributionof subtypes according who classification reported were: well differentiated in 32%, myxoid in 38%, pleomorphic in 10%, dedifferentiated in 8% and mixed in 12%. According to FNCLCC grading system(4), grade 1 was described in 40% of cases, grade2 in 26% of cases and grade3 in 34% of cases. The table 1 summarize demographic, clinicopathologic features, therapeutic managementand outcomesof our cohort.

Forty-six patients were treated (92%) with limb sparing surgery. The margins were clean (R0) in 65.2% of the cases, microscopic involvement (R1) was found in 6.5% of the cases and 28.3% of patients had macroscopic involvement (R2). Second surgery was performed in 17 cases (wide excision in 63.7% and amputation in 36.3%). Twenty-seven patients (54%) received adjuvant radiotherapy with an average of 10 weeks after surgery. The mean dose were 54 GY. A salvage radiotherapy (dose: 50 GY) was performed in 6 patients who underwent a second surgery for involved margins.

Chemotherapy was indicated in 8 patient (16%):adjuvant CT in 37.5%, pre-operative CT in 25% and palliative CT in 37.5%.

Relapses were reported in 20 cases (40%) with an average delay of 11 months [1-108]: locoregional relapse in 9 cases, distant relapse in 7 cases and both distant and locoregional relapse in 4 cases. The site of metastases was the lung in 50%, the bone in 10% in and the liver in 20%.

The 5 and 10 years OS were 52% and 38%, respectively (figure1). Survival was significantly correlated to the histologic subtype of LS tumors. In fact, the 5 years OS was 82% in well differentiated, 61% in myxoid, 50% in mixed and 0% in pleomorphic and dedifferentiated ($p=0.002$). The 5 and 10 years OS was 81% and 60% for grade 1 respectively, and 10% and 0% for grade 3 respectively ($p=0.0001$). Radiotherapy increased theOS from 40% to 70% at 5 years and from 29% to 43 at 10 years ($p=0.063$). In case of relapse, the 10 years OS decreased from 73% to 19% ($p=0.062$).The OS was not associated to the tumor size ($\leq$10 or >10 cm) ($p=0.746$) nor the quality of resection ($p=0.761$).

The 2 and 5 years DFS were 36% and 19%, respectively (figure2). The one year DFS was 35% for patients with tumors $\leq$10cm and 0% for tumors >10cm ($p=0.013$). By the histologic subtype, the one year DFS was 36% for pleomorphic and 0% for myxoid and dedifferentiated ($p=0.005$). The high grade decreased significantly the 2 years DFS from 37% in case of grade1 to 0% for the grade 3 ($p=0.0001$). Involved surgical margins decreased the one year DFS from 10%to 0% ($p=0.0001$).

In multivariate logistic regression, the independent predictive factors of metastases were high grade ($p=0.036$) and involved margins ($p=0.005$). The age ($p=0.637$), tumor localization ($p=0.421$), tumor size ($p=0.166$), histological subtype ($p=0.108$), chemotherapy ($p=0.453$) and radiotherapy ($p=0.152$) were not predictive factors of distant metastases.

IV. Discussion

LS usually occurs in adults between the ages of 40 and 60 years with a slight predominance of men(5). In our series, the median age was 50, with a female predominance (sex ratio 0.78). However, LS may occur at any age and remains a ubiquitous tumor with greater frequency for the thigh(1,6). Swelling is the most frequently or even unique revealing symptom(7).

Contrary to LS, the other soft tissue sarcomas are more likely to be larger but remains asymptomatic because of their deep localization, which leads to delayed diagnosis(6–8). In our cohort, the mean tumor size was 14 cm. the same mean tumor size of LS was reported by kim and al (9). This is also in accordance with the results the large cohort of 801 cases of LS studied by Dalal and al who reported 15 cm as a mean tumor size (10).

According to the WHO classification of soft tissue sarcomas, the LS presents 4 different histological types: well differentiated, myxoid, pleomorphic, dedifferentiated and mixed LS represent (11). This heterogeneity of the different histological types is also reflected in the survival rates and is frequently reported in the literature(12).

In our study, the most frequently described histological subtypes were the well-differentiated (32%), and myxoid(38%). Pleomorphic,dedifferentiated and mixed were reported in 10%, 8% and 12% respectively. Dalal and al described a 5-years disease specific survival of 93% for well differentiated and of 92% for myxoid LS. Whereas this rate decreased to 44% in case of dedifferentiated subtype, 74% for round cell and 59% for pleomorphic(10). Knebel and al reported a 5 and 10 years OS rates of 100% and 82.1% in well differentiated LS; this rates decreased to 57.2% and 40.1% in dedifferentiated LS(13). In our study, the 5 years OS was 82% in well differentiated, 61% in myxoid, 50% in mixed and 0% in pleomorphic and dedifferentiated.

In our cohort, the 5 and 10 years OS was 81% and 60% for grade 1 respectively, and 10% and 0% for grade 3 respectively; the high grade decreased significantly the 2 years DFS from 37% in case of grade1 to 0% for the grade 3. For Kim and al, high grade LS decreased the 1-years DFS survival from 83.3% to 44.4% in case of (9). The recent study of Knebel and al showed a significantly improvement of OS rate in patients with grade 1 LS comparing with patients with grade 2 and 3 LS (13). These findings were also in line with the data published by Roque and al (14), and Lietman and al (15).

Tumor size has been described as a prognostic factor of the survival rates.Zagars and al, suggested that tumor size >5 cm was significantly associated to survival and metastatic rates in patients with LS (16). Knebel and al reported that patients with tumor size smaller than 5 cm had prolonged OS comparing to those with a greater tumor size: 80% versus 67.3% (13). Kim and al, suggested the cut off of 10cm for the median tumor diameter was significantly correlated to the OS without an impact on DFS(9). In our study, the 5 years OS was not associated to the tumor size (with a cut-off value of 10 cm). However, the one year DFSwas 35% for patient with a tumor size less than 10cm and 0% for patients withgreater than 10cm.

Although sarcomas appear well limited by a capsule, the microscopic disease is often beyond the pseudocapsuleso wide excision is necessary to achieve a complete resection(17). In fact, the quality of the margins has been described as one of the main prognostic factors of survival. Kim and al, described an improvement of the 5-years OS from 88.1%, to 75% in case of microscopically positive margins compared to negative margins(9). The same authors described a significant decrease to 44% in case of macroscopically involvement.Dalal and al, suggested that gross margin status was an independent predictor of disease specific survival rates (10). In our study, involved surgical margins decreased the one year DFS from 10% to 0% but was not associated the OS. This is in accordance with Eilber and al findings (18).

It has been suggested that the association of radiotherapy to limb-saving surgery may improve local controland reduce the rate of amputation (16,19).In our study, radiotherapy increased the OS from 40% to 70% at 5 years and from 29% to 43% at 10 years. In contrary, Kim and al didn't find a survival benefit of adjuvant radiation therapy for patients with LS (9). However, subgroups analysis find a benefit in the 5 years OS from the administration of adjuvant radiotherapy in low grade LS (well differentiated and myxoid). The new ESMO-EURACAN guidelines of 2018, recommend as a standard treatment of STS with high grade, deep localization and tumor size >5cm, adjuvant radiotherapy after surgery (1).

The benefit of administering chemotherapy whether for localized or locally advanced soft tissue sarcomasaimed essentially to improvethe survival rates.These indications mainly targeted the patients with sarcoma at high risk of subclinical micrometastases. Eilber and al reported a survival benefits from adjuvant chemotherapy for primary extremity LS with tumor size greater than 5 cm and high-grade (18). In our study, the risk of metastatic relapses was not reduced with the administration of chemotherapy. This disparity in the benefit of chemotherapy in LS tumors could be explained by the heterogeneity of the sensitivity to chemotherapy according to the histological subtypes(20). In fact, Jones and al, described a higher response rate to chemotherapy with myxoid/round cell liposarcoma 48% versus 11% in well-/ dedifferentiated liposarcoma.Indications of adjuvant chemotherapy remains controversial because of the lack of evidence of the benefit; it could be optional for LS tumors >5 cm with high grade and deep localization but never in the intention to palliate to an incomplete surgery(1). However, the pre-operatively CT could be administrated in locally advanced tumors in order to improve resectability(1).

The limitations of our study was the retrospectiveand uni-centric character, the limited number of patients, and the initial intake of some patients by non-oncologist surgeons, which led to subsequent surgical re-excisions.

V. **Conclusion**

LS of the limbs represents a real therapeutic challenge for the surgeon, radiotherapist and oncologist due to the rarity of the reported data. Although complete surgical resection remains the only curative treatment of all the STS, radiotherapy and chemotherapy could be useful especially for the prevention and the treatment of relapses. However, the choice of the treatment modalities must consider the different prognostic factors specific to each histological types. Larger series and more accurate genetic assessment could lead to a personalized treatment.

Conflicts of interest: None

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TABLE1: Clinicopathologic features of patients with LS

characteristics		N	%
Gender	**Men**	22	44
Women		28	22
Age, years	**≤40**	18	36
40-65		23	46
>65		9	18
Delay of consultation, months	**≤12**	27	54
>12		23	46
Site	**Upper limb**	11	22
	Lower limb	39	78
Size, cm	**≤ 5**	3	6
	5-10	16	32
>10		31	62
Histological subtypes	**Well differentiated**	16	32
	Myxoid	19	38
	Pleomorphic	5	10
	Dedifferentiated	4	8
	Mixed	6	12
Grade	**1**	20	40
	2	13	26
	3	17	34
Surgery	**Yes**	46	92
	No	4	8
Margins quality	**R0**	30	65.2

	R1	3	6.5
	R2	13	28.3
Radiotherapy	**Yes**	27	54
	No	23	46
Chemotherapy	**Yes**	8	16
	No	42	84
Relapse after surgery	**Local**	9	18
	Metastatic	4	8
	Local and metastatic	7	14

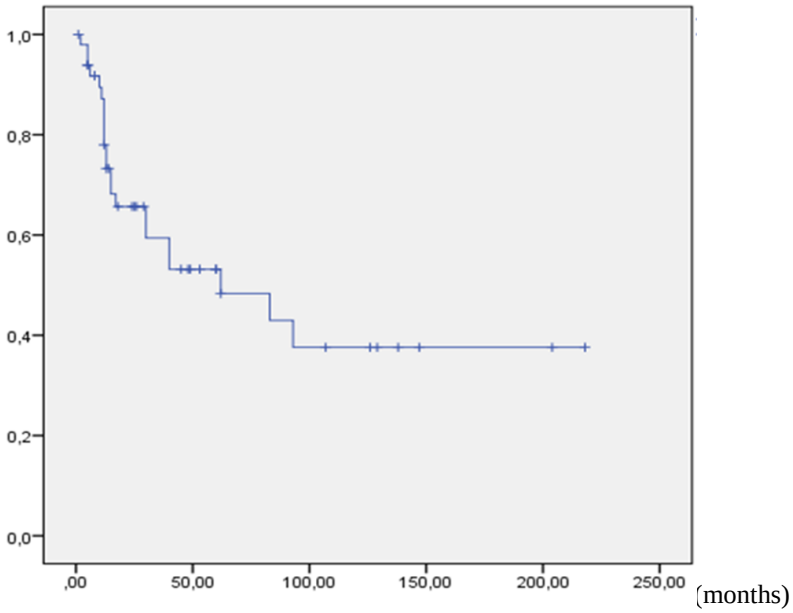

Figure 1: Kaplan-Meier curves of overall survival for patients with LS of the limbs.

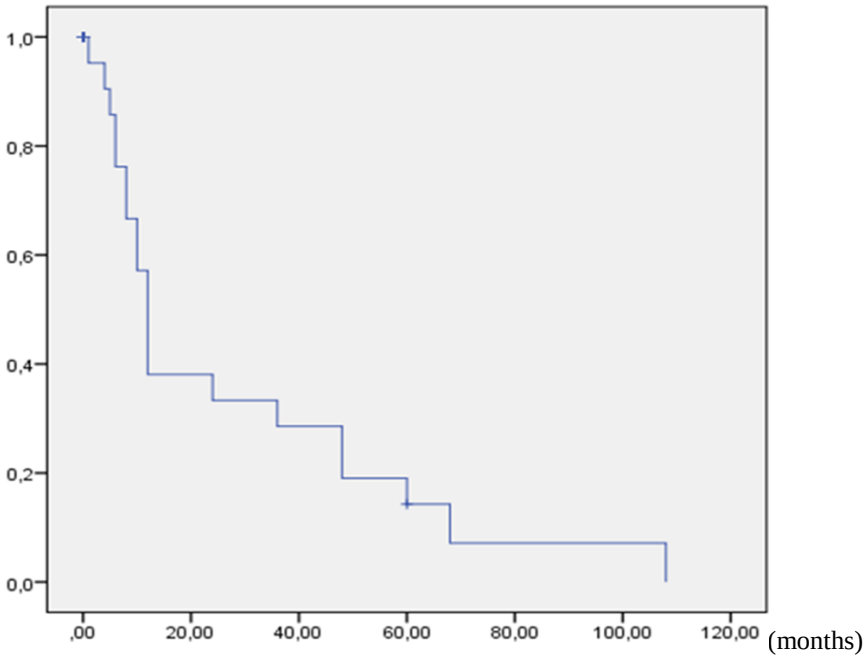

Figure 2: Kaplan-Meier curves of RFS for patients with LS of the limbs.

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