Leiomyosarcoma: Clinicopathological study and retrospective analysis of prognostic factors in a series of 100 patients

Francesco Muratori^{a,*}, Daniela Greto^c, Mauro Cenatiempo^a, Giacomo Mazzei^a, Filippo Frenos^a,
Giuliana Roselli^b, Lorenzo Livi^c, Rodolfo Capanna^d, Giacomo Baldi^d,
Domenico Andrea Campanacci^a

^a Divisione di Ortopedia Oncologica e Ricostruttiva Azienda Ospedaliero Universitaria Careggi Firenze, Italy

^b Divisione di Radiologia Azienda Ospedaliero Universitaria Careggi Firenze, Italy

^c Unità di Radioterapia Azienda Ospedaliero Universitaria Careggi Firenze, Italy

^d Divisione Oncologia Ospedale Prato, Italy

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ABSTRACT

The Authors reported a retrospective study of 100 Leiomyosarcoma (LMS), evaluating factors that may influence Overall Survival (OS), Local Recurrence Free Survival (LRFS), Metastasis Free Survival (MFS). Tumor Size ($P = 0,0009$), Local Recurrence ($P = 0,0487$), Distant relapse ($P < 0,0001$), Type of Presentation ($P = 0,0213$) were significant risk factors affecting overall survival (OS). Tumor Size ($P = 0,024$), age at diagnosis ($P = 0,0086$), type of presentation ($P < 0,0001$) and Local Recurrence ($P = 0,0152$) affected metastasis free survival (MFS). Type of presentation ($P = 0,001$) was an independent prognostic factor of local recurrence-free survival (LRFS).

1. Introduction

Leiomyosarcoma is a malignant neoplasm showing pure smooth-muscle differentiation and is an excellent example of tumor with different biology and prognosis depending on anatomic site. LMS is one of the most representative histology of retroperitoneal (including pelvic) sarcomas and is the predominant histology arising from large blood vessels. It is less common, accounting for 10–15% of limb sarcoma. LMS of the extremities arise more frequently in the lower limbs, but may develop elsewhere. LMS usually have intramuscular and subcutaneous localizations in approximately equal proportions, and few times originate from a small to medium-sized vein¹.

The typical histological pattern of LMS is that of intersecting, sharply margined fascicles of spindle cells. This pattern may be less well-defined in some tumours, and occasionally there is a focal storiform, palisaded, or haemangiopericytoma-like arrangement.¹ LMS of soft tissue are capable of both local recurrence and distant metastasis. The therapy of choice involves surgical resection with negative margins. The most important prognostic factors affecting clinical outcome are tumour location, size, histological grading, margin, age, clinical presentation, local recurrence and metastasis.^{1–6}

The aim of our retrospective study was to evaluate factors that may

influence Overall Survival (OS), Local Recurrence Free Survival (LRFS) and Metastasis Free Survival (MFS) in a series of patients diagnosed with LMS of the limbs treated in a single centre.

2. Materials and methods

We retrospectively reviewed histological and clinical records of 100 patients treated between 1990 and 2015. Mean age was 61,5 years (range = 28–84), 98 (98%) LMS localized in the limbs and 2 (2%) in the dorsal muscle.

All data collected included patient characteristics (age, gender), tumor characteristics (site, size, type of presentation, clinical symptoms, stage, histology), diagnostic and therapeutic procedures (type of biopsy, type of surgery, margins, neoadjuvant and adjuvant therapy) and clinical outcome. This research has been approved by the IRB of the authors' affiliated institutions.

The data were obtained from the patient's medical records. Local recurrence and distant metastasis were recorded. Each patient underwent anamnestic collection of his medical history, physical examination and routine blood tests, electrocardiogram and chest X-ray were obtained. Considering that plain x-ray or CT were not useful to identify the features and the edges of the primary tumor, MRI was performed in

* Corresponding author. Largo Palagi 1, Firenze, Italy.

E-mail address: fmuratori@inwind.it (F. Muratori).

most patients. MRI was particularly useful in defining certain characteristics such as homogeneity, necrosis, haemorrhagic areas, the local spread of the disease (size) and tumor stage. To complete the diagnostic work up Chest CT scan, bone scan or PET (from 2009) were performed preoperatively.

Type of presentations were divided in primary lesions (VG), local recurrence (LR), radicalization or additional wide excision of LMS managed with inadequate excision in other centers (RSD) and in patients with metastases at onset (MET)) (Table 1). All patients with a local recurrence or inadequate excision were originally treated in other Institutions.

Histological diagnosis was confirmed by open biopsy, ultrasound-guided needle biopsy or previous inadvertent excision performed at other centres.

Microscopical surgical margins were classified in wide and radical, marginal and intralesional. The surgical approach was the main treatment that attempt to get wide margins. When the tumor was adjacent to critical structures such as nerves, blood vessels or bones, a planned marginal surgery has been accepted.

Radiotherapy (RT) in preoperative or postoperative setting was performed in patients with high grade disease or tumor size > 5 cm, deep sited tumors or in case of close/positive margins.

External beam radiotherapy was delivered with 6–10 MeV photons, 3DCRT (3D conformal radiotherapy) was performed before 2011, thereafter all treatments were delivered by Helical Tomotherapy. GTV (Gross Tumor Volume) was obtained contouring the surgical bed or the gross tumor in case of preoperative RT on T1 weighted MRI images, CTV (Clinical Target Volume) derived from an expansion of 1.5 cm radially and 4 cm longitudinally from the GTV, and finally 0.5 cm were added to the CTV to obtain the PTV (Planning Target Volume). A total dose of 50 Gy and 60–66 Gy in preoperative and postoperative setting, respectively. A standard fraction schedule was used: 2Gy per fraction, 5 days a week.

Chemotherapy was performed in patients with more than two of these unfavourable prognostic factors: high grade disease, tumor size > 5 cm, deep sited tumours, positive surgical margins. It consisted of 3 or 5 cycles of Epirubicine (60 mg/m² Day 1–2) and Ifosfamide (3 g/m² Day 1–3) administered every 21 days.⁷ Granulocyte colony-stimulating factor was administered to prevent neutropenia. The patients were followed every 3 months for the first 3 years, every 6 months for the following 2 years and annually thereafter.

The statistical analysis was performed with MedCalc software version 16.8.4. Values of $P \leq 0,05$ were considered statistically significant. All variables were analyzed for their impact on overall survival, local recurrence-free survival and metastasis-free survival with a follow-up of 5 and 10 years from surgery time. In univariate analysis of the overall survival estimates, local recurrence-free survival and metastasis-free survival were calculated according to the method of Kaplan-Meier.

The comparison of survival curves calculated was performed by the long-rank test media. The hazard ratios and confidence intervals (95%) were calculated using the Cox hazard test. Significant results parameters univariate analysis were included in a multivariate Cox regression model.

3. Results

Our data included 61 (61%) primitive LMS, 6 (6%) local recurrences of primitive LMS, 22 (22%). Tumor sites were: lower extremities in 77 (77%) cases, upper limbs in 21 (20%) cases and trunk in 2 (2%) cases (Table 1). Specifically 6 LMS (6%) were localized at shoulder muscles, 10 (10%) at the arm, 5 (5%) at the elbow and distal to the elbow, 6 (6%) in pelvic muscles, 46 (46%) in the thigh and 25 (25%) in the knee and distal to the knee. Two LMS (2%) were localized in the muscle of the trunk. The preoperative MRI showed size > 10 cm in 18 (18%) patients, between 5 and 10 cm in 38 (38%) patients, and < 5 cm in 44 (44%) patients (Table 1). 13 (13%) tumors were classified low grade

Table 1

Main features.

Characteristics	N°	%
Patients	100	100
Presentation:		
Primary (VG)	61	61
Local recurrence (LR)	6	6
Radicalization (RAD)	22	22
Metastatic LMS (MET)	11	11
Grading (FNCLCC):		
Low grade	13	13
High grade	87	87
Site:		
Lower limb	77	77
Upper limb	21	21
Trunk	2	2
Size:		
> 10 cm	18	18
5–10 cm	38	38
< 5 cm	44	44

and 87 (87%) high grade (Table 1). At the final histology 87 (87%) LMS were treated with radical or wide excision, 13 (13%) with marginal excision (Table 2). 46 cases received postoperative radiotherapy (7 cases with size > 10 cm, 20 cases between 5 and 10 cm, 19 high grade LMS with dimensions < 5 cm), of which 5 patients had not adequate margins at histological examination and in 40 patients with high-grade LMS (FNCLCC grading system) (Table 2).

Chemotherapy was administered in 27 patients with high grade LMS, 1 patient received neoadjuvant chemotherapy and 26 post-operative chemotherapy (Table 2).

The mean follow-up was 74 months (range 1–246 months), 51 patients had a follow up longer than 5-years.

3.1. Local recurrence

We observed 20 (20%) local recurrences with mean disease free interval of 63 months (range 1–207 months) (Table 2). LRFS was 88% at 5 years and 84% at 10 years.

Sixteen LMS treated with radical or wide excision developed local recurrence, 6 with size > 10 cm, 6 with size between 5 and 10 cm and only 4 with sizes < 5 cm. Seven patients with local recurrence underwent amputation for involvement of neurovascular bundle, nine patients were treated with excision.

Four LMS treated with marginal excision developed local recurrence, 2 with size > 10 cm, 2 with size between 5 and 10 cm. All local recurrences were treated with amputation for involvement of neurovascular bundle.

At univariate analysis only type of presentation (local recurrence of tumors treated in non-specialized cancer center had a higher risk to develop new local recurrences) ($P = 0,001$) is risk factor for local recurrence-free survival (LRFS) (Fig. 1), while at multivariate analysis we did not observed significative factor.

3.2. Distant metastasis

We observed forty-two (42%) patients with metastases, of which 11 had metastatic disease at the onset, while 31 developed metastases after surgery (Table 2). 24 primitive LMS (39%) that developed metastases were treated with wide resection and 7 (11%) with marginal surgery. The site of metastases were lungs in 25 (60%) patients, bones (above all spine) in 7(16%) and multiple sites in 11(26%) patients, respectively. Seven (35%) local recurrences developed distant metastases thereafter.

MFS was 55% and 50% at 5 and 10 years, respectively.

At univariate analysis Size ($p = 0,024$) (Fig. 2), age ($p = 0,0086$) (Fig. 3), type of presentation ($p < 0,0001$) (Fig. 5) and Local Recurrent disease (0.0152) (Fig. 4) were prognostic factors affecting metastasis

Table 2
Margin, radiotherapy, chemotherapy, local recurrence, metastasis.

	Wide/Radical	Marginal	Intralesional
Margin	87	13	0
	Preoperative (50 Gy)	Postoperative (60–66 Gy)	
Radiotherapy	0	46	
Chemotherapy	Neoadjuvant	Adjuvant	
	1	27	
Local recurrence	20 (16%)	16 (wide/radical excision), 4 (marginal excision)	
Metastasis	42 (42%)	11 onset mts, 24(wide/radical surgery), 7 (marginal surgery)	
Site metastasis	25 pulmonary, 7 bone, 11 multiple site

Fig. 1. Presentation represent a significant risk factor ($P = 0,001$) in local recurrence free survival (LRFS).

Fig. 3. Age is a significant risk factor ($p = 0,0086$) in metastasis free survival (MFS).

Fig. 2. Size is a significant risk factor ($p = 0,024$) in metastasis free survival (MFS).

Fig. 4. Local Recurrence is a significant risk factor ($p = 0,0152$) in metastasis free survival (MFS).

free survival (MFS).

In multivariate analysis for MFS size ($p = 0.0051$), age ($p = 0,0165$) and presentation ($p = 0,0168$) were statistically significant, unlike the event local recurrence ($p = 0.0742$).

3.3. Overall survival

OS was 69% and 60% at 5 and 10 years, respectively.

At univariate statistical analysis Size ($p = 0,0009$) (Fig. 6), recurrent disease ($p = 0,0487$) (Fig. 7), distant Metastases ($p < 0,0001$) (Fig. 8), presentation ($p = 0,0213$) (Fig. 9) were prognostic factors affecting Overall Survival.

At the multivariate analysis for OS, size ($p = 0,0071$) was significant and metastasis is higher significant ($p < 0,0001$).

4. Discussion

LMS are uncommon tumors and with a well known poor long-term prognosis. In our report overall survival was 69% and 60% at 5 and 10 years, respectively. Svarvar et al. reported a series from Scandinavian Sarcoma Group of 225 LMS patients; the authors recorded a cumulative survival of 49% at 10 years.² Our metastasis incidence was 42%. Previous analyses from other institutions reported a higher incidence of metastases from 29.4% to 44.7%.²⁻⁵

Size was a negative prognostic factor, in our experience, affecting OS ($p = 0,0009$) and MFS ($p = 0,024$). LMS with size < 5 cm had a better prognosis than LMS with size between 5 and 10 cm and > 10 cm at 5 and 10 years. The importance of large tumor size as an adverse prognostic factor on OS and MFS was in line with earlier studies on soft tissue LMS and other histopathologic sarcoma types. Different Authors

Fig. 5. Type presentation is a higher significant risk factor ($p < 0,0001$) in metastasis free survival (MFS).

Fig. 8. Metastasis is a higher significant risk factor ($p < 0,0001$) in overall survival (OS).

Fig. 6. Size is a significant risk factor ($p = 0,0009$) in overall survival (OS).

Fig. 9. Type of presentation is a significant risk factor ($p = 0,0213$) in overall survival (OS).

Fig. 7. Local recurrence is a significant risk factor ($p = 0,0487$) in overall survival (OS).

described a correlation between size, metastasis and survival and these data could be explained with a higher possibility of micro-metastasis.^{2,3,5,6,8}

We observed better results on OS, LRFS and MFS in LMS performed the initial operation at our institute than local recurrences after a surgery in other not specialized centres and metastatic LMS at the onset. Additional wide excision of LMS managed with inadequate excision in other centres had better LRFS (94% at 5 and 10 years). Surgical excision should be carefully planned by experienced surgeons considering the areas in proximity of vascular structures, nerves and bone.^{9,10} The treatment of LMS in facilities no-specialized in cancer care is an important risk factor for local recurrence. Chandrasekhar et al. reported

59% of local recurrences on 363 cases of soft tissue sarcoma treated inadequately.¹⁰ This finding is also confirmed by our data: local recurrence of tumors treated in non-specialized cancer center had a higher risk to develop new local recurrences ($p = 0,001$), distant metastases ($p < 0,0001$) and reduced overall survival ($p = 0,0213$).

In contrast with other studies surgical margins in our experience are not negative prognostic factors on survival, even if we treated 87% of LMS with adequate surgery vs 13% with no-adequate margins (marginal surgery). Harati et al. did not observe in their series of 164 patients correlation of margins with LRFS, DSS, e OS.¹¹ In Memorial Sloan-Kettering Cancer Center series, including abdominal and retroperitoneal LMS, positive margins did not have adverse impact on OS, but were associated with reduced LRFS.⁴ Several retrospective studies on extremity soft tissue sarcomas presented similar results and could not reveal a prognostic significance of negative margins on survival.^{12,13} Kandel et al. published a meta-analysis including 32 retrospective and prospective studies, most studies failed to establish a strong correlation between surgical margins and OS suggesting that tumour characteristics other than margin status are important.¹⁴ Nevertheless, these findings are in contradiction to several large studies as well that determined a beneficial prognostic impact of negative margins on LRFS and OS.^{15–17} Scandinavia Sarcoma Group and Abraham reported that positive margins adversely affected the local outcome but did not influence OS.^{2,18}

The cumulative incidence of our local recurrence is 16% with a mean disease free interval of 63 months (range 1–207 months). This is consistent with previous study of similar primary sites. Gladly observed 10% of incidence of LR in extremity and truncal patients, all of which occurred within 5 years of resection.⁴ Miyajima et al. observed 8% LR

rate and all recurrences occurred within 2 years from resection.⁶ We observed higher incidence of metastases in forty-two (42%) patients, of which 11 were really metastatic at the onset, while 31 developed metastases after surgery. Lung was the most common site of metastasis, a finding that has been previously reported.^{3,19,20} The second most common site of metastasis was bone in seven cases and 11 in multiple site. Local recurrence was a negative prognostic factor in our series on OS ($p = 0,0487$) and MFS ($p = 0,0152$). The strongest determining factor related to death was the presence of metastases in our series ($p > 0,0001$), as reported by other Authors.²

In one series, elderly patients with age > 60 had a much higher incidence of metastasis during follow-up, however, the reasons for this observation are unclear. Surely physiological changes associated with aging, comorbid medical conditions, psychosocial factors, functional and nutritional status, and polypharmacy are several key issues that require careful consideration in elderly patients with cancer.²¹

In several studies histologic grading was a negative prognostic factor.^{3,5,22} Abraham et al. identified the histologic grade and tumor depth as independent factors predicting OS.¹⁸ We did not observe a correlation between grading and survival, even if 87% LMS were high grade, and only 13% low grade.

Radiation and chemotherapy had not showed beneficial prognostic effects or did not assess its impact, in accordance to other studies on somatic LMS.^{2,4,11,18} These data are according with our experience however adjuvant radiation has been determined to control local disease in non-visceral soft tissue sarcomas in general. In a prospective study of 2014 conducted by the National Cancer Institute in Bethesda 141 patients with extremity STS were included, it was found that patients who underwent limb-sparing surgery with adjuvant radiation had an improved LRFS compared to patients who underwent surgery without radiation.²³

Doxorubicin or the association Doxorubicin/Ifosfamide are the backbone of first line treatment for advanced inoperable and metastatic disease, so a number of agents have emerged as effective second and third line options including gemcitabine/docetaxel, trabectedin and pazopanib,^{24,25} but the role of adjuvant chemotherapy remains controversial.

This study has some limitations: 1) it is a retrospective study, even though performed on a consecutive series of patients treated at a single Institution by the same surgical team; 2) This study includes patients treated over the long term of 25 years during which chemotherapy and radiotherapy therapies have changed drastically, but despite the evolution of therapies wide surgical excision remains the treatment of choice, particularly in non-metastatic forms 3) Our series included primary LMS together with local recurrence, radicalization after inadequate surgery performed elsewhere, metastatic LMS and type of presentation resulted correlate with the outcome.

In conclusion, this study provides data that may help clinicians estimate the prognosis of patients with extremity LMS. Adverse prognostic features included elder age, large tumour size, presentation of LMS, local recurrence and metastasis. The data from this study could not underscore the benefit of negative margins achieved at the resection of the primary tumour, while the local recurrence at presentation of LMS treated in no-specialized cancer center seems to have worse results and prognosis. Radicalization of LMS treated in other centre before knowing diagnosis showed better prognosis. Chemotherapy and radiotherapy do not seem have beneficial prognostic effects.

Conflict of interest

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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