

Primary leiomyosarcoma of bone: a clinicopathologic and immunohistochemical study of 142 cases

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Summary

Leiomyosarcoma is a rare malignant mesenchymal tumor characterized by smooth muscle differentiation. It typically arises in both visceral and somatic soft tissues, while involvement of bone being exceptionally uncommon. Although primary leiomyosarcoma of bone has been a subject of ongoing debate, the advent of immunohistochemistry has reduced the misclassification of other sarcomas, such as fibrosarcoma and undifferentiated pleomorphic sarcoma, facilitating the accurate identification of true primary LMSB cases. To date, just over 200 well-documented LMSB cases have been published in English-language literature. Despite this, understanding of its clinical behaviour and factors influencing patient outcomes remains limited. In this study, we present the clinical, pathological, and immunohistochemical findings from 142 cases of primary bone leiomyosarcoma including extended follow-up data.

Key words: Primary bone sarcomas, leiomyosarcoma, malignant mesenchymal tumor, rare bone tumor

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Introduction

Leiomyosarcoma is a rare malignant mesenchymal tumor featuring smooth muscle differentiation that typically arises in both visceral and somatic soft tissues ¹. Visceral sites include the gynaecological tract, the gastrointestinal tract, and, only rarely, the bone. The existence of primary leiomyosarcoma of bone (LMSB) has been a topic of significant debate for many years. Historically, most of these lesions were in fact classified either as malignant fibrous histiocytoma (MFH) or fibrosarcoma (FS) ²⁻⁵. The term MFH has since been abolished and replaced by undifferentiated pleomorphic sarcoma (UPS) for both bone and soft tissue sites ¹. Furthermore, the current WHO classification mostly considers FS a diagnosis of exclusion, reserved for spindle cell malignancies of bone that exhibit a herringbone architecture and lack specific lineage of differentiation. With the advent of immunohistochemistry, the incidence of both FS and UPS diagnoses has significantly decreased, leading to a clearer identification of sarcomas that typically arise in the soft tissues but present as primary tumours of bone ⁶⁻⁸.

To date, a little over 200 well-characterized cases of LMSB have been reported in the English literature through case reports and small case se-

ries⁹⁻¹⁸. However, our understanding of its clinical behaviour, prognostic, and predictive factors remains extremely limited due to the few studies providing comprehensive clinical information. Diagnosing primary LMSB – particularly through biopsy – poses a significant challenge because of its rarity and morphological diversity, both of which contribute to diagnostic uncertainty.

Herein, we describe the clinical, histopathologic, and immunohistochemical features of 142 cases of primary leiomyosarcoma of bone with long-term follow-up. This study aims to identify potential prognostic and predictive factors that may guide future clinical management and therapeutic approaches.

Materials and methods

INCLUSION CRITERIA

Since 1937, all clinical charts, imaging, histological slides, and tissue blocks of all primary bone sarcomas treated at “Istituto Ortopedico Rizzoli” have been collected. Based on morphology, immunohistochemistry, and molecular features we recently reclassified a group of 418 primary tumor of bone previously diagnosed as: 177 FS (42.3%), 172 UPS/MFH (41.1%), 39 LMSB (9.3%), 15 hemangiopericytomas (3.6%), 13 malignant peripheral nerve sheath tumours (MPNST) (3.1%), 1 synovial sarcoma (0.3%), and 1 liposarcoma (0.3%).

All cases with a prior history of soft tissue or visceral sarcoma, or those lacking complete clinical information, were excluded. For all included cases, radiologic imaging was reviewed by an expert radiologist to confirm the bone origin. Adequate histological material for revision was available for all cases. Clinical information was collected, including sex, age at diagnosis, anatomic site, and the presence of metastasis at onset. Additionally, data on treatment, follow-up, and patient outcomes were analysed.

The diagnosis of leiomyosarcoma was made according to the current criteria of the World Health Organization Classification of Tumours of Soft Tissue and Bone¹. Surgical margins were defined using the Enneking score system¹⁹. Wide surgical margins were considered adequate (negative), while marginal and intralesional margins were considered inadequate (positive).

A total of 142 cases of LMSB were included in the study. In the attempt to correlate morphology with outcome, all cases were stratified according to the FNCLCC three-tier grading system²⁰. Following the initial statistical analysis the cases in the series were divided into two morphological grades: low and high. High-grade LMSB included tumours classified as G2

and G3 according to the FNCLCC system, while low-grade LMSB corresponded to G1 cases.

To confirm the diagnosis, immunohistochemical analysis for smooth muscle actin (monoclonal antibody 1A4, Ventana, prediluted), desmin (monoclonal antibody DE-R-11, Ventana, prediluted), and h-caldesmon (monoclonal antibody h-CALD, Ventana, prediluted) was performed. At least two out of the three muscular markers were present to substantiate the diagnosis of leiomyosarcoma. In all cases we also performed immunostains for myogenin/Myf4 (monoclonal antibody EP162 Ventana, prediluted), SATB2 (monoclonal antibody SATBA4B10, 1:200/ Santa Cruz Biotechnology), MDM2 (monoclonal antibody IF2, Invitrogen Carlsbad, CA), H3K27me (monoclonal antibody C36B11, 1:200 Cell Signaling), SS18–SSX (rabbit monoclonal antibody, clone E9X9V; Cell Signaling Technology, Danvers, MA, USA) and SSX (clone E5A2C; cat. no. 23855; Cell Signaling Technology). All beforementioned immunohistochemical markers were negative in the case series. Four µm-thick paraffin embedded tissue sections were cut for each case, heated at 58°C for 2 hours, deparaffinized and immunostained on a Ventana Bench Mark following the manufacturers' guidelines (Ventana Medical Systems, Tucson AZ, USA). The sections were stained with antibodies reported in the Table I

Table I. Source of dilution and antigen retrieval of the antibodies used.

Antibodies	Clone	Dilution/Antigen retrieval
CK AE1/AE3	AE1/AE3/PCK26	Prediluted/Ventana
Smooth muscle actin	1A4	Prediluted/Ventana
Desmin	DE-R-11	Prediluted/Ventana
EMA	E29	Pre-diluted/Ventana
h-Caldesmon	h-CALD	Pre-diluted/Ventana
Myogenin	EP162	Pre-diluted/Ventana
S100	4C4.9	Pre-diluted/Ventana
GFAP	EP672Y	Pre-diluted/Ventana
ERG	ERP3964	1:100/ Ventana
CD31	JC70	Pre-diluted/Ventana
MDM2	IF2	1:50/ Invitrogen, Carlsbad, CA
CD34	QBEnd-10	pre-diluted/Ventana
ERG	ERP3964	1:100/Ventana
ALK	ALK01	Pre-diluted/Ventana
SATB2	SATBA4B10	1:200/ Santa Cruz Biotechnology
STAT 6	S-20, SC-621	Santa Cruz Biotechnology
H3K27me3	C36B11	1:250/ Cell Signaling Technology
SS18-SSX	E9X9V	1:500/ Cell Signaling Technology
SSX	E5A2C	1:500/ Cell Signaling Technology

and antibody detection was performed using Ultra View Universal DAB Detection Kit (Ventana Medical Systems, Tucson AZ, USA). Pretreatment for antigen retrieval was performed at 95°C with Tris-EDTA, pH 8 for 20 minutes. When necessary, endogenous tissue peroxidase was blocked by treating the sections with 0.3% H₂O₂. The slides were stained with hematoxylin, then rehydrated, and coverslipped. Appropriate positive and negative controls were included in each run.

STATISTICAL ANALYSIS

Disease-free survival (DFS) and overall survival (OS) were estimated by Kaplan-Meier survival functions. For each subgroup of patients defined by clinical and pathological features (age: adolescent and young adult (AYA $\leq$ 39) versus adult (40 or older), gender, margins, histological grade, and use of chemotherapy) the point survival estimates at 5 and 10 years since surgery with their 95% confidence intervals were obtained. Log-rank tests of equality of the survival functions at 5 and 10 years were also conducted. Multivariable Royston-Parmar survival models with different functions (proportional hazards, proportional odds and probit) and 1 to 5 degrees of freedom were obtained including the above mentioned clinical and pathological features as covariates; among these models, the one with the best fit to data according to BIC and AIC indices was chosen. All analyses were carried out using Stata v.17.0, with statistical significance set at $p = 0.05$.

The study was approved by the Ethical Committee of IRCCS Istituto Ortopedico Rizzoli (protocol #CE2496). All patients provided informed written consent.

Results

In this study, we examined 142 well-characterized cases of primary leiomyosarcoma of bone. Our reclassification of UPS/MFH and FS of bone revealed LMSB as the most common histotype, accounting for 48% of cases²¹⁻²².

CLINICAL FEATURES AND FOLLOW-UP

The study cohort consisted in 57 females and 85 males, with a median age at diagnosis of 45 years (range 8-83 years). The median follow-up was 87 months (ranging from 2 to 390 months). The lower extremities were most commonly affected, accounting for 73% of cases, with the majority of tumours located in the femur (50%) or tibia/fibula (23%). The upper extremities represented 27% of cases, with the humerus (14%) and the spine/sacrum (13%) being the most in-

volved sites. Twenty-seven patients (19%) presented with metastases at onset. Although documented in literature, in our series no cases of LMSB were identified in the craniofacial bones.

According to the AJCC TNM 8th edition pathologic staging system, leiomyosarcomas were most common in stage 2 (68%). Specifically, all high-grade LMSB cases were classified as stage 2 or 3, while low-grade LMSB cases were exclusively stage 1.

Surgical resection was performed in 88 out of 142 (62%) patients. Margins were reported as wide, marginal and intralesional in 71, 12, and 5 cases, respectively. Major resection (amputation) was carried out in 39 patients, of whom 37 had wide margins and 2 had marginal margins, while curettage was conducted in 7 patients. According to the Enneking score system, margins were adequate in 122 out 134 operable cases. Eight patients with locally advanced tumours were considered inoperable.

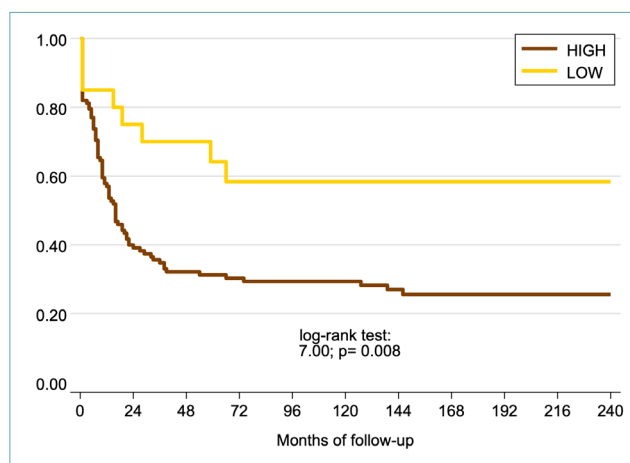
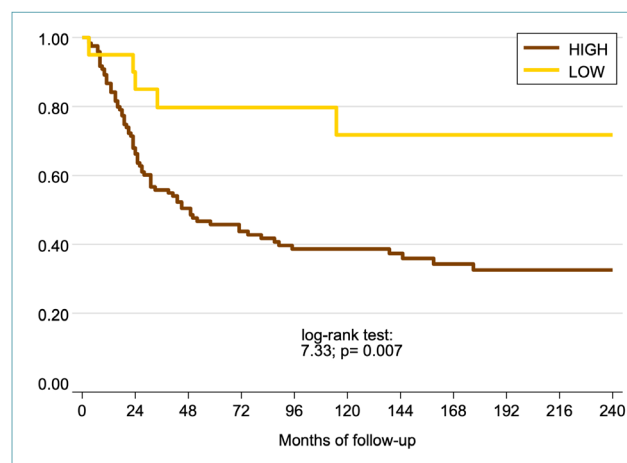
Radiotherapy was carried out in 13 patients, including 3 receiving it after resection, 5 after curettage, and 5 among inoperable patients. Systemic chemotherapy was administered in 79 patients. The most common therapeutic protocols included regimens containing Adriamycin, Cisplatin, Ifosfamide $\pm$ Methotrexate. Furthermore, 29 patients received additional adjuvant chemotherapy. Among the 79 patients who received preoperative chemotherapy, histologic response ranged from 10 to 99%. Over 90% tumor necrosis was observed in 4 patients (14%) of the series, 2 of whom were treated with a combination of Adriamycin, intra-arterial Cisplatin, and Methotrexate, while the remaining 2 received Adriamycin, Cisplatin, and Ifosfamide. Conversely, 7 patients showed $\leq$ 30% tumor necrosis. Among these, 5 were treated with a combination of Methotrexate, Adriamycin, Cisplatin, and Ifosfamide; 1 with Adriamycin, Cisplatin, and Ifosfamide; and 1 patient received a Ewing-like chemotherapy regimen.

Local recurrences were observed in 26 cases (18%). During follow-up, metastases occurred in 60 cases (42%). The lung was the most common site of metastasis (37 cases), followed by the bone (10 cases), lymph nodes (2 cases), and soft tissues (1 case), while 10 patients developed both lung and bone metastases.

The overall survival (OS) ranged from 2 to 390 months, with 5-year and 10-years OS of 50.6% and 43.3%, respectively (Tab. II). A statistically significant prognostic difference was observed when comparing low-grade LMSB with high-grade LMSB ($p = 0.007$) (Fig. 1 and Fig. 2). However, no significant difference in OS was found between tumours classified as grade 2 and grade 3 according to the FNCLCC sys-

Table II. 5-year and 10-year disease-free and overall survival rates of the 142 patients affected by leiomyosarcoma included in our cohort.

	N (%)	Disease-free survival (DFS)						Overall survival (OS)					
		5 –year DFS %	95% CI	Test; p-value*	10– year DFS %	95% CI	Test; p-value*	5 – year OS %	95% CI	Test; p-value*	10– year OS %	95% CI	Test; p-value*
All patients	142 (100)	36.0	28.0-44.0		33.5	25.7-41.5		50.6	41.8-58.7		43.3	34.6-51.7	
Age													
< 30 years	36 (25.3)	47.2	30.5-62.3	0.604	44.3	27.8-59.5	0.461	54.5	36.9-69.2	0.329	51.3	33.8-66.4	0.516
30-59 years	69 (48.6)	34.2	23.0-45.6		30.9	20.2-42.3		52.3	39.7-63.5		43.9	31.6-55.5	
≥60 years	37 (26.1)	27.0	13.5-42.4		27.0	13.5-42.4		43.1	26.0-59.2		31.5	14.5-50.1	
Gender													
Female	57 (40.1)	42.5	29.3-55.0	0.157	38.4	25.6-51.1	0.057	62.0	47.3-73.6	0.999	50.1	35.2-63.2	0.066
Male	85 (59.9)	31.4	21.8-41.6		30.1	20.5-40.2		43.4	32.5-53.8		39.1	28.4-49.6	
Margins§													
adequate	123 (86.6)	38.8	30.1-47.4	0.349	36.0	27.5-44.6	0.712	53.5	44.1-62.1	0.338	46.3	36.8-55.2	0.892
inadequate	12 (8.5)	29.2	7.2-56.1		29.2	7.2-56.1		45.8	16.9-71.0		34.4	9.2-61.9	
Chemotherapy													
yes	79 (55.6)	43.6	32.4-54.2	0.376	42.1	30.9-52.8	0.393	57.6	45.5-67.9	0.067	52.7	40.5-63.4	0.332
no	63 (44.4)	26.5	16.1-37.9		22.9	13.3-34.2		41.6	29.0-53.7		31.4	19.7-43.8	

**Figure 1.** Kaplan-Meier curves and log-rank tests of disease-free survival. A statistically significant difference was observed between high and low-grade LMSB ($p = 0.008$).**Figure 2.** Kaplan-Meier curves and log-rank tests of overall survival. A statistically significant difference was observed between high and low-grade LMSB ($p = 0.007$).

tem. Overall survival did not appear to correlate with surgical margin status, gender, age, and tumor size. However, improved DFS and OS were reported for

patients who underwent chemotherapy. In fact, the 5 years OS in patients treated with chemotherapy was 57.6% (Fig. 3).

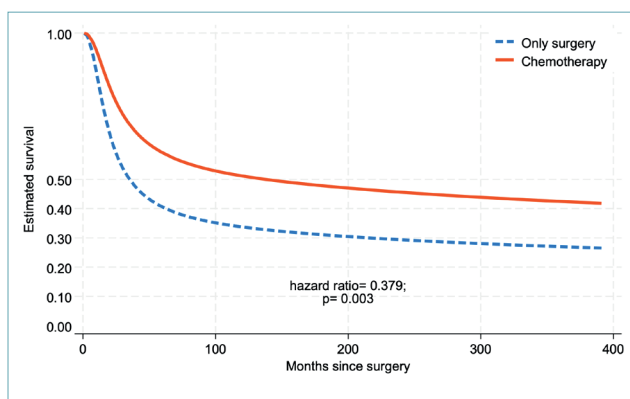


Figure 3. Overall survival estimated by multivariable Royston-Parmar model. The graph shows a statistically significant estimated OS difference between patients receiving systemic chemotherapy and patients treated solely by surgery ($p = 0.003$).

IMAGING

The majority of tumours involved the long bones of the extremities and were located in epiphysis (2%), metaphysis (21%), diaphysis (26%), metaepiphysis (30%), or metadiaphysis (21%). All lesions appeared lytic on radiography, with sclerotic features observed in 17 cases (Fig. 4A). The cortex was consistently broken-through, and soft tissue involvement was present in all but 2 cases (Fig. 4B). Longitudinal periosteal bone formation was observed in 42 cases, while

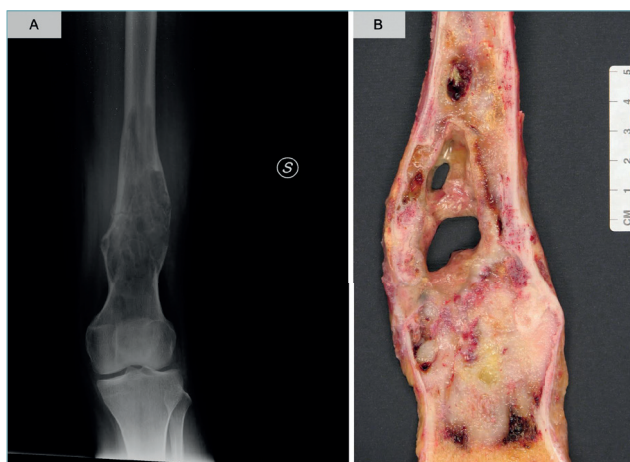


Figure 4. Radiograph (anterior-posterior view) shows a lytic lesion with well demarcated borders. The tumor breaks trough of the cortex (A). Gross specimen features a well-demarcated grey-white mass with haemorrhagic and necrotic areas, focally extending in the surrounding soft tissue (B).

perpendicular bone formation was seen in 3 cases. Multiple lesions were identified in 31 cases. Notably, imaging in 4 lesions mimicked a giant cell tumor of bone, presenting as an eccentric lytic lesion involving the epiphysis of a long bone.

HISTOLOGY AND IMMUNOPHENOTYPE

Histologically, most cases were characterized by the presence of intersecting long fascicles of variably atypical spindle cells featuring fibrillary eosinophilic cytoplasm and blunt-ended nuclei (Fig. 5A, 5B). Approximately 20% of cases displayed highly atypical pleomorphic cells, often associated with areas featuring more conventional spindle cell morphology. In purely pleomorphic tumours, myogenic differentiation was confirmed by the expression of smooth muscle immunophenotypic markers. No areas of epithelioid morphology were observed in the series; however, scattered multinuclear osteoclastic-like cells was frequently identified.

Areas of necrosis were present in 40% of cases, with necrosis typically involving less than 50% of the tumoral area. Mitotic index ranged from 5 to 20 mitotic figures per 2 mm², with a mean of 8 mitosis per 2 mm². According to FNCLCC grading system, 66 LMSB cases (46.5%) were classified as grade 3, 56 (39.4%) as grade 2 and 20 (14.1%) as grade 1. Based on the two-tier grading system, 122 cases were classified as high-grade and 20 as low-grade.

By immunohistochemistry, LMSB variably expressed smooth muscle actin (93%), desmin (37%), and h-caldesmon (43%) (Fig. 5C and 5D). At least focal expression of two out of these three smooth muscle differentiation markers was observed in all cases. Myf4 and S100 were negative in all tumours, whereas cocktail cytokeratin AE1/AE3 and EMA were positive in 11 and 3 cases, respectively.

Discussion

Leiomyosarcoma is a malignant mesenchymal tumour exhibiting morphologic and immunophenotypic features of smooth muscle differentiation. Typically, leiomyosarcoma arises in the deep soft tissue of the extremities or within the wall of medium-large size vessels of retroperitoneum. Other frequent sites include the skin and visceral organs, particularly the gastrointestinal tract. Additionally, leiomyosarcoma is the most frequent sarcoma in the gynaecological region. Although primary LMSB is exceedingly rare, it represents the most frequent histotype among non-osteogenic, non-chondrogenic, and non-Ewing sarcomas occurring in bone^{6,22}. The true incidence of LMSB has historically been un-

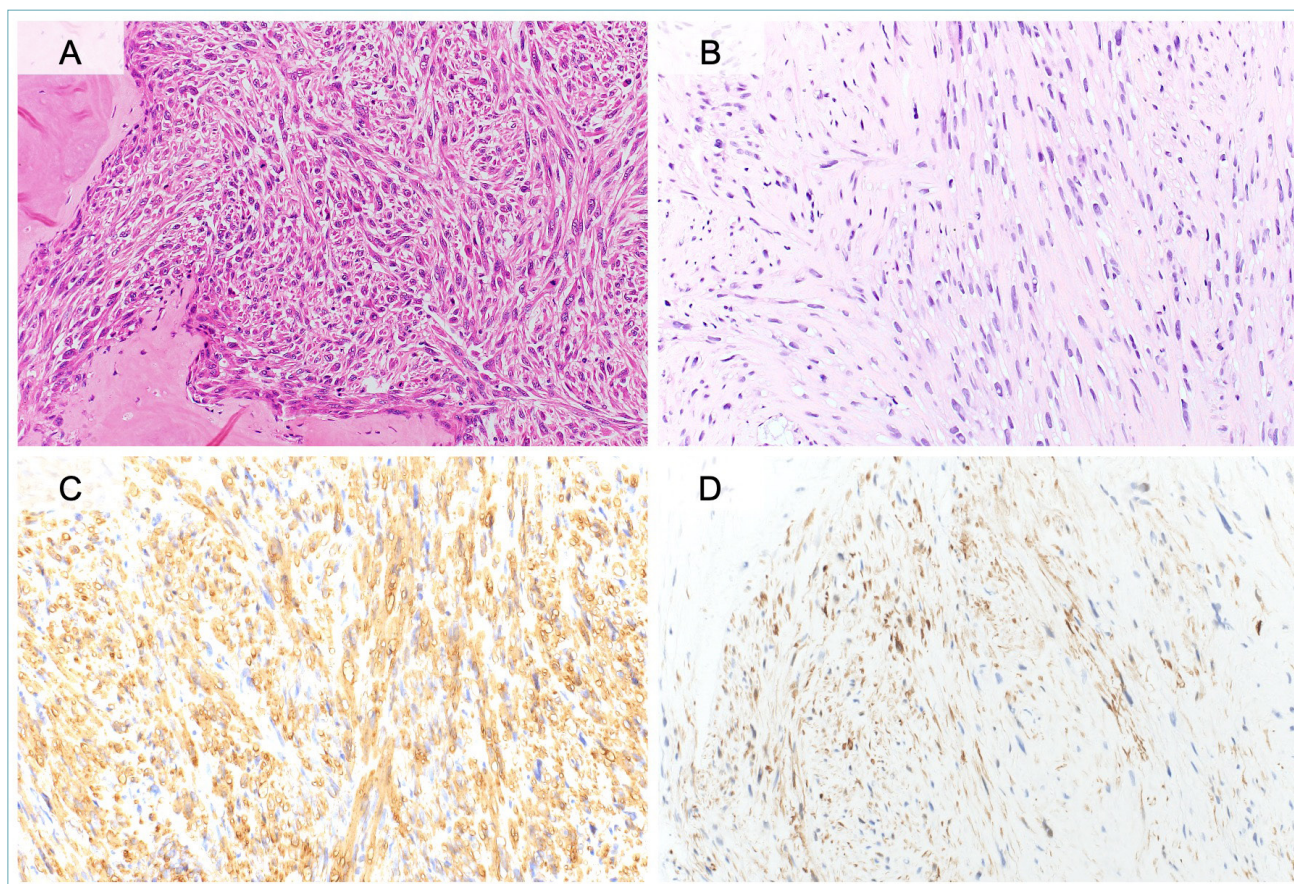


Figure 5. Primary leiomyosarcoma of bone is composed of variably atypical spindle cells proliferation featuring fibrillary eosinophilic cytoplasm and blunt ended nuclei with evident bony infiltration (A: high grade LMSB; B: low grade LMSB) (H&E, original magnification, x200). The spindles cells show variable immunopositivity for smooth muscle actin (B), caldesmon and desmin (D).

derestimated, as demonstrated in our series where 47% of cases were previously misdiagnosed as UPS/MFH, FS, or myofibroblastic sarcoma. The availability of immunohistochemical techniques has undoubtedly improved the accuracy of LMSB diagnosis.

Our series confirmed that LMSB exhibits a male predominance, with a peak of incidence occurring in the fifth decade of life. Notably, we excluded any patients with a prior history of uterine leiomyosarcoma. Generally, the tumours occurred in the long bones of the lower extremities, followed by the upper extremities, with the meta-epiphyseal region being the most frequently involved site. Interestingly, while the literature reports craniofacial bone involvement in up to 20% of cases, no such occurrences were observed in our series²³⁻²⁵. Radiographically, LMSB did not present specific features. In most cases, it appeared as a centrally located, ill-defined lytic lesion with cortical bone disruption and extension into the surrounding soft tissues. In rare

instances, imaging revealed an eccentrically placed epiphyseal lesion in the long bones, mimicking a giant cell tumor of bone (GCT).

Previous studies have described LMSB arising in association with pre-existing conditions or prior treatment, including radiotherapy and chemotherapy^{9,26}, Paget's disease²⁷, orthopaedic implants²⁸ and bone infarcts²⁹⁻³⁰.

In the vast majority of cases within our series, we were able to reanalyse both the initial biopsy and the surgical specimen. Our data indicate that integrating morphologic and immunohistochemical features (variable combination of expression of smooth muscle actin, desmin, and h-caldesmon) allows for the accurate recognition of LMSB on core biopsies, resulting in a high concordance with the surgical specimen. Since the expression of myogenic markers alone is alone insufficient for a definitive LMSB diagnosis, it is essential to evaluate them in the context of the tumour's morphology.

The key histological features include a spindle cell proliferation organized in long fascicles, with eosinophilic fibrillar cytoplasm and blunt-ended nuclei. Diagnosing purely pleomorphic lesions is noticeably more challenging, making the expression of muscular markers even more critical. In our series, at least two smooth muscle markers were positive in all cases, with SMA being the most frequently expressed. While marker expression may be strong and diffuse, particularly in low-grade tumours, high-grade tumours often exhibited focal and weak staining. We have considered any degree of marker expression as positive.

Immunohistochemistry is also vital for distinguishing LMSB from other pleomorphic mesenchymal lesions in bone, such as pleomorphic rhabdomyosarcoma (RMS) and UPS. Myogenin was absent in all cases, thus excluding the possibility of pleomorphic RMS. Additionally, low-grade LMSB may present with osteoclast-like giant cells, which could lead to diagnostic confusion. When LMSB occurs as an eccentric lesion in the epiphysis of long bones, it may mimic radiologically a giant cell tumor (GCT). However, GCT typically lacks spindle cell morphology and giant cells are far more abundant than in LMSB. In addition, GCT of bone is usually negative for smooth muscle markers and positive for H3F3A.

Low-grade central osteosarcoma may also be considered in the differential diagnosis, however, it is characterized by permeative bone destruction exerted by a SATB2 positive low-grade spindle cell proliferation typically harbouring *MDM2* gene amplification. In our series, all LMSB were negative for both *MDM2* and SATB2.

Eighty-six percent of cases were classified as high-grade tumours. We observed a statistically significant prognostic difference in OS between G1 and G2-G3 tumours when using the three-tier FNCLCC grading system, although no significant difference was noted between grade 2 and grade 3. As expected, when applying a two-tier grading system a statistically significant difference clearly emerged.

The 5-year DFS and OS rates were 30% and 39%, respectively, for high-grade LMSB, compared to 64% and 79%, respectively, for low-grade LMSB. The clinical behaviour of LMSB is generally aggressive, particularly in the setting of metastatic disease, and optimal management should be determined by multidisciplinary teams at sarcoma referral centres. Consistent with the established treatment approach for localized disease, surgical resection was the preferred treatment in our series, with most cases achieving adequate margins. Clinical outcomes did not correlate with surgical margin status, gender, age, or tumor size. Although multiple bone lesions were observed in

rare cases, their presence did not represent a negative prognostic factor.

The role of chemotherapy and radiotherapy in LMSB remains controversial, as numerous studies have failed to demonstrate a significant difference in survival benefit^{10,18}. In our series, chemotherapy appeared to have some impact on improving OS. Among the 29 patients who underwent neoadjuvant therapy, 14% showed a good treatment response (defined as > 90% tumor necrosis). The neoadjuvant regimen included a combination of drugs generally used for osteosarcoma. It is important to note that this is a small and heterogeneous cohort of patients with broad age range (8-71 years; median 33 years), resulting in variations in treatments combinations and drug dosages^{31,32}. A large, multicentre prospective study is necessary to accurately evaluate the role of chemotherapy in LMSB. In conclusion, we present the largest case series of LMSB treated at a single institution with exceptionally long-term follow-up. Through the application of strict clinical, immunohistochemical and morphological criteria, our findings suggest that the true incidence of this exceptionally rare primary bone tumor is higher than previously reported. Histological grade remains the most important prognostic factor, with a two-tier system providing better statistical prognostic differentiation. While surgical resection continues to be the preferred treatment, our data indicate a potential benefit from systemic therapies, supporting their consideration in the management of LMSB.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

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AUTHORS CONTRIBUTIONS

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by A. Righi, M. Gambarotti, G. Magagnoli, M. Sbaraglia, T. Frisoni, E. Palmerini and A. P. Dei Tos. Molecular analysis was performed by S. Benini, S. Cocchi and G. Gamberi. Statistical analysis was done by D. Gibertoni. The draft of the manuscript was written by M. Sbaraglia, A. Righi, M. Gambarotti, E. Palmerini and A. P. Dei Tos. All authors read and approved the final manuscript.

ETHICAL CONSIDERATION

This manuscript meets the ethical standards. Specific informed consent is routinely obtained.

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