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Leiomyosarcoma of the extremity deep soft tissues: analysis of factors predictive of survival and imaging features

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Abstract

Objective: This study aimed to report the visual outcomes of deeply located Leiomyosarcoma (LMS) in the extremities and treatment results.

Methods: The histological diagnosis of each case was confirmed by the pathology council and only cases with LMS localized in the deep soft tissue of the limb were included in this study. Treatment-related factors such as all the visual features of the tumor, type of therapy, local and distant recurrence, follow-up time, and outcome were analyzed. Overall survival time was determined.

Results: Evaluation was made of 17 patients, comprising 11 females and 6 males with a mean age of 64.35 years (range, 52-75 years). The localization of the primary lesion was the lower extremity in 14 patients (82.34%), and the upper extremity in 3 (17.34%). The average size of the lesions was 8.23 cm (range, 3-22 cm). All lesions were staged according to the TNM Classification of soft tissue sarcomas, as 3 (17.64%) patients in stage IIA, 9 (52.94%) in stage IIB, and 5 (29.41%) in stage IV. In the radiological features of the lesions, only two patients had scattered calcification and osseous pathology in the tumor tissue. The signal properties obtained in other soft tissue sarcomas on magnetic resonance images (MRI) were also present in these lesions. Neoadjuvant chemotherapy was applied to 5 of 17 patients, and surgical and adjuvant radiotherapy was applied to the remaining 12 patients. These patients were followed up for an average of 66 (23-111) months. Local recurrence occurred in 3 patients. The five-year disease-free survival rate was 58.8%, and the disease-survival rate was 64.7%.

Conclusion: The most important result of this study was that the only effective factor on overall survival is tumor size ($p < 0.001$). Neoadjuvant chemotherapy was not seen to have any significant effect on this disease.

Keywords: Leiomyosarcoma, deep soft tissues, cancer

Introduction

Leiomyosarcoma (LMS) is a malignant neoplasm characterized by histological differentiation of smooth muscle cells and is divided into three groups as cutaneous LMS, gastrointestinal and uterine LMS, and somatic LMS (1). These three groups should be considered as separate clinical entities due to different clinical behavior, different treatment, and different prognosis. Somatic LMS is often seen in the retroperitoneum, the soft tissue of the extremities, blood vessels, and occasionally in the bone. Although a rarely diagnosed tumor in the past, this sarcoma has started to be diagnosed more frequently with advances in histological diagnosis, especially in immunohistochemistry. Nevertheless, despite all these advances, histological diagnosis is still difficult because of the heterogeneity of soft tissue sarcomas, (2-4).

It is currently claimed that LMS constitutes 8-16% of non-visceral soft tissue sarcomas, but there is limited information about these tumors seen in deep soft tissues of the limbs (5,6). Although there is currently a relative increase in incidence, there are not enough data about the visual properties and treatments of these sarcomas localized in deep soft tissue, especially in the extremities. Wide resection has been specified as the gold standard for the treatment of these tumors, but there is no consensus on the treatment modality. In particular, controversy continues over the effects of adjuvant treatments and the way they are applied. This study aimed to present information about the visual properties, treatments and clinical outcomes of LMS with deep soft tissue location in a limb of 17 cases treated and followed up in our clinic.

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Material and Methods

The histological diagnosis of each case was taken into consideration by the pathology council and the LMS included in this study were histologically confirmed and localized in deep soft tissue that had not previously been exposed to radiotherapy. All tumors included in the study were confirmed based on positive immunohistochemical staining (IHCS) for smooth muscle actin and desmin, and morphology showing smooth muscle differentiation. Data were recorded of patient gender, age at the first visit, location of the primary tumour, tumor size, staging, and the presence of metastasis at the time of diagnosis. The analysis was also made of treatment-related factors, including all the visual features of the tumor, local therapy type, systemic chemotherapy, local and distant recurrence, follow-up time and outcome. Overall survival and disease-free survival time were determined.

The study was approved by the Local Ethics Committee and the procedures adhered to the tenets of the Declaration of Helsinki. Informed consent was obtained from all patients.

Results

The evaluation was made of 17 patients with LMS located in limb deep soft tissue, diagnosed between 2002 and 2018. From the initial enrolment, 5 patients were excluded due to the lack of a final follow-up examination or specimens were determined as suspected diagnosis by the council, and 1 patient who started neoadjuvant chemotherapy but underwent amputation due to the progression of the tumor. The 17 patients comprised 11 females and 6 males with a mean age of 64.35 years (range, 52-75 years). On first presentation, all patients had complaints of swelling and pain. The primary lesion was localized in the lower extremity in 14 patients (82.34%), in the thigh region in 11 (64.70%), and the lower leg in 3 (17.34%). The primary lesion was located in the upper limb in the arm area in 3 (17.34%) patients. All lesions were staged according to the TNM Classification of soft tissue sarcomas, as 3 (17.64%) patients in stage IIA, 9 (52.94%) in stage IIB, and 5 (29.41%) in stage IV. Tumor size (in cm) was defined as the largest size of the tumor in the surgical sample reported by pathologists. The average size of the lesions was 8.23 cm (range, 3-22 cm).

Radiological properties

X-ray: Scattered calcification and severe destruction of the distal femur were detected in the tumor tissue of 2 patients. In one patient, new cortical bone formation was noted in the distal femur secondary to the large soft tissue mass. This patient had minimal cortical destruction and no medullary invasion. A pathological fracture was determined in one patient (Figure 1).

CT: Changes in bone tissue were determined in 2 patients. In addition to a very large soft tissue mass, one of these patients had new cortical bone formation and minimal cortical destruction in the distal femur, and no medullary invasion. The other patient had cortical destruction, medullary infiltration, and pathological fracture in addition to the large soft tissue mass. No appearance of calcification or ossification was observed in any of the other 15 patients.

MRI: MRI was obtained from all patients, including T1A, T2A, fat-suppressed sequences, and contrast images. The lesions were seen to have relatively regular borders and intramuscular localization. There were signals of medium to low on T1-weighted images and heterogeneous hyperintensity on T2-weighted images. Heterogeneous hyperintense signals were dominant on fatty images. Hyperintense signals were received, especially in the central area of the lesion. High contrast agent uptake was seen on the contrast images, with more evident contrast involvement in the periphery of the lesions, and minimal or absent involvement in the central regions (Figure 2,3).

Treatment type

Of the 17 patients included in the study, 5 received neoadjuvant therapy. RT was administered to these 5 patients in addition to chemotherapy. In total, 5 patients were using ifosfamide, doxorubicin, gemsutab, and docetaxel chemotherapeutic agents. In the remaining 12 patients, the only radiotherapy was applied as an adjuvant in their first treatment.

The surgical margin was defined according to the International Cancer Control Association (UICC) classification. Accordingly, resection was performed as R0 in 14 patients, R1 in 2 patients, and R2 in 1 patient. In 2 cases with secondary bone invasion of a soft-tissue leiomyosarcoma, tumor prosthesis was applied. The necrosis rate of patients receiving neoadjuvant therapy was 45% (40-60%) on average, histopathologically. No tumor necrosis rate was obtained over 90% in the resected specimen of any patient.

All 12 patients with localized disease had at least two operations. One of these patients went to amputation. All five patients with distant metastases at the time of admission did not receive secondary surgery due to advanced age and comorbidity.

Oncological results

These patients were followed up for an average of 66 (14-111) months. Local recurrence occurred in 3 patients, 2 of which had distant metastasis at the first presentation. All of these patients had both chemotherapy and radiotherapy. The surgical margins of patients with local recurrence were R0 in one and R1 in two. The five-year disease-free survival rate was 58.8%. The disease survival rate was 64.7%. All patients with metastasis died within an average of 18 (14-49) months from first admission.

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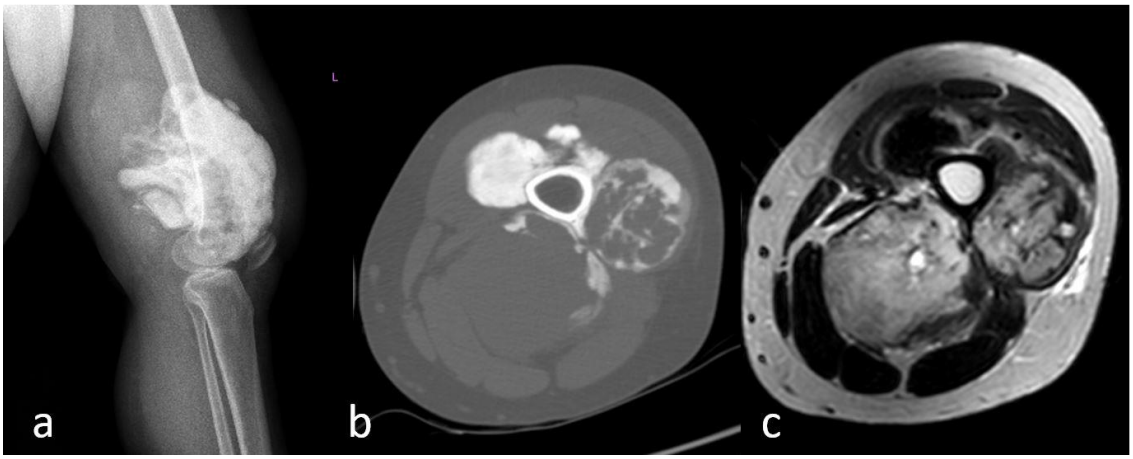

Figure 1. The x-ray and CT images of the mass showing calcification and new bone construction and not showing infiltration of the medulla in the distal metaphysioepiphysial region of the femur **(a-c)**.

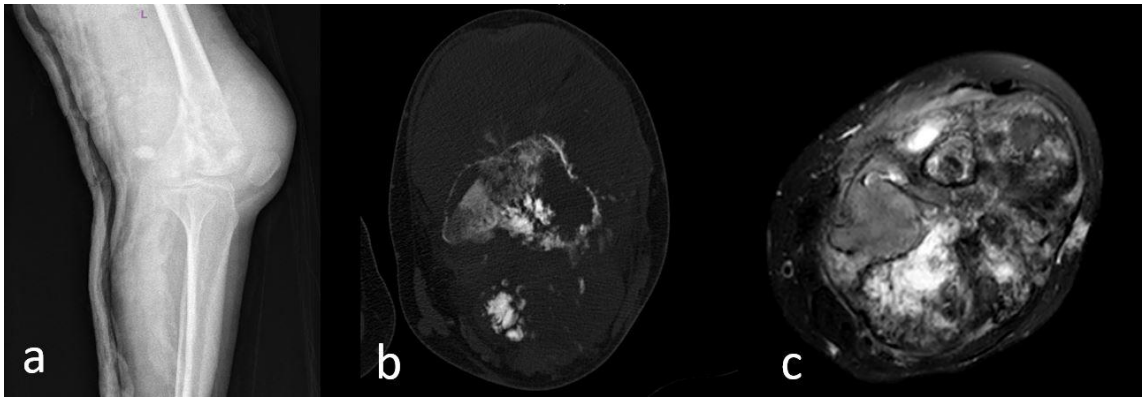

Figure 2. Another patient with a large soft tissue component causing cortical destruction and medullary infiltration in the distal femur **(a-b)**. A large mass with a heterogeneous signal in the axial T2W + FS image of the same patient **(c)**.

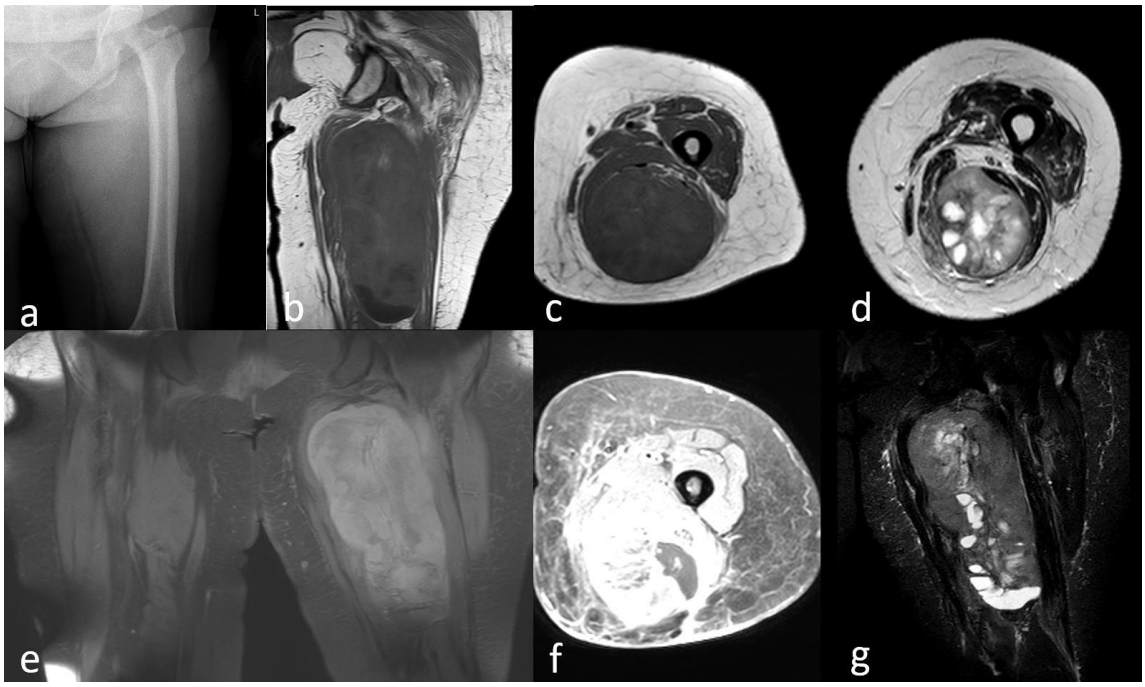

Figure 3. A 63-year old female patient presented with complaints of swelling in the posterior of the left thigh. **(a)** Increased soft tissue density in the thigh posterior region on the plain radiograph. There was no calcified or ossified lesion and no pathology in the bone tissue. **(b, c)** Heterogeneous hypointense lesion localized in a relatively well defined smooth muscle with deep location on MR, T1W images, **(d)** Heterogeneous appearance with a hyperintense signal especially in the central region, **(e, g)** Heterogeneous hyperintensity on STIR images, **(f)** contrast-enhanced central hypointense signal-dense lesion with intense contrast enhancement.

Discussion

LMS is defined as the most common soft tissue sarcoma that constitutes 10% of non-visceral soft tissue sarcomas, although this rate has not been determined with large series and meta-analytical studies. Current advances in both visual technologies and histopathological diagnostic tools have importance for the correct diagnosis and identification of this tumor. Therefore, new studies are needed on the frequency and rate of occurrence of this tumor.

However, the visual properties of deep-seated soft-tissue LMS of the limb have not been detailed as yet. Although the visual properties of primary osseous LMS have been partially defined, there are insufficient data about the visual properties of soft tissue LMS and the pathologies they create in bone tissue. The visual features of primary osseous leiomyosarcoma are defined as an aggressive osteolytic appearance, accompanied by endosteal erosion, and fine periosteal reaction. Soft tissue extension is very rare and if it is present, is minimal (7-9). Pathological fracture has only been reported rarely. Primary leiomyosarcoma is most common in the long bones of the lower extremities, especially the distal femur (8). Although internal calcification foci have been reported in these tumors in some studies (10), no internal calcification or ossification pathologies were encountered in the current study, except for the increase in soft tissue density. However, in two of the current study cases, in addition to the very large soft tissue mass, in one case there was noticeable cortical destruction and medullary invasion, while in the other case, minimal cortical destruction but not medullary invasion were detected on the images. In this last case, a wide periosteal serous bone formation was detected. It was not unusual for LMS, which originate from either soft tissue or bone, to display this type of image. To the best of our knowledge, there have been no previous reports of cases showing such a radiological feature. However, these two facts are controversial. These two cases were defined as LMS originating from soft tissue because they had a very large soft tissue component, and did not show radiological features resembling those of primary osseous LMS. In the MR images obtained in this study, the signals obtained were similar to those of general soft tissue sarcomas, with no different or specific visual data detected.

No consensus has been reached as yet on the treatment approaches for LMS, and there are insufficient data in the literature, especially regarding the effectiveness of chemotherapy. Studies conducted on heterogeneous groups with limited cases have provided different opinions. Some authors have reported that neoadjuvant chemotherapy has little effect on these tumors (11-13), while others have stated that the combination of trabectedin plus doxorubicin, and eribulin is effective (14-16). Unfortunately, many of those studies are related to visceral LMS. In the current study, adjuvant therapy was added to the surgical treatment of all 17 patients. Neoadjuvant chemotherapy was applied to 5 of 17 patients, and chemoradiotherapy was added after surgical treatment for these 5 patients, all of whom had lung metastasis on the first presentation. The surgical resection limits of these patients were evaluated as R0 in 4 patients and R1 in 1. The histopathological necrosis rate of the total resection specimens of these patients applied with neoadjuvant therapy was mean 45% (range, 40-60%). Satisfactory necrosis rates could not be obtained in any of these cases. The chemotherapy regimen was continued postoperatively due to the distant metastasis. Two of these patients developed local recurrence within the first year. A combination of surgery and adjuvant radiotherapy was applied to all 12 patients without distant metastasis. Surgical resection limits were obtained of R2 in 1 of these patients, R1 in 1, and R0 in 1. Local recurrence occurred in only one of these patients.,

In total local recurrence developed in 17.64% (3/17) of the patients. The surgical margin was R0 in two of these patients with local recurrence, and all had lung metastasis and chemoradiotherapy at the time of initial admission. In addition, the preoperative tumor size of two patients with local recurrence was 20 cm in one and 17 cm in the other. The other patient with local recurrence was the patient with the first surgical limit of R2. In that patient, local recurrence occurred in the re-resection despite a negative margin. The most prominent feature in patients with local recurrence was tumor size and patient age. All patients were in the geriatric age group and tumor size was >17 cm in all patients. Although a negative limit was obtained in 82.35% (14/17) of the current study patients, local recurrence occurred in 17.64%. The prominent feature of this study is that a negative limit was obtained, but recurrence developed in two cases where metastasis was present on admission. Some authors have stated that although positive margins adversely affected the local outcome, OS was not affected and thus, the quality of surgical margins only had an impact on local control (17,20,21). Due to the low number of cases in this study, it is not possible to make a definitive comment in this regard. However, the result obtained from the current study does not correspond to the above-mentioned view. Although the surgical margin is an important factor in local control, the degree of aggressiveness and size of the tumor also seem to be two important factors.

Soft tissue LMS with deep localization in the extremity are tumors with high metastatic potential. Distant metastasis rates have been reported as 23.3-44.7% in previous studies (17-20). In the current study, distant metastasis was determined in 5 patients on first admission, and later in another 2 (16.66%) of the other 12 patients. The time to development of metastasis was 32 months on average. All patients with distant metastasis died within an average of 18 months from first admission. Of the two patients who developed metastasis later, 1 died 55 months after treatment, and the other at 65 months.

In previous studies, histological grade, tumor size, and depth have been reported as important factors for disease-specific survival (DSS) (20). In the multivariate analysis of a study by Abraham et al. (21), histological grade and tumor depth were determined to be independent factors predicting OS. In a multi-institutional analysis by the Scandinavian Sarcoma Group (SSG), Svarvar et al. (17) evaluated the surgical outcomes of 225 patients with somatic LMS and found that tumour grade, size, and depth correlated significantly with OS in univariate analysis. It is

difficult to draw a conclusion about these parameters in the current study as all the tumors were high-grade with deep localization. However, the results of the study showed that tumor size was the most significant factor in overall survival. (p <0.001) Advanced age (p = 0.743) was not significant in overall survival.

Conclusion

In conclusion, although soft-tissue leiomyosarcomas are rare tumors in the extremities, they usually present as well-circumscribed or ill-defined, large, heterogenous soft tissue masses on CT and MRI. In 1 of the 17 patients in this study with biopsy-proven leiomyosarcoma, both cortical disruption and medullary invasion were apparent on CT and MRI. In another patient there was seen to be a feature that caused minimal cortical erosion and did not cause medullary invasion. However, in that tumor, there was a new peripheral bone formation in the distal femoral region. Therefore, it should be kept in mind that on CT and MRI, soft tissue leiomyosarcomas may simulate other malignant lesions such as osteosarcoma and metastases. To the best of our knowledge, gross cortical and medullary destruction has not been previously reported in extremity soft tissue leiomyosarcomas. When prognostic factors for local recurrence, distant metastasis, and overall survival were examined, overall survival was seen to be short, especially in all patients with distant metastasis and comorbidity. However, in the statistical analysis, it was determined that the only factor with an effect on overall survival was tumor size. Another important point of the study was the development of the opinion that chemotherapy has no significant effect on this disease. The patients with the longest overall survival were those with a tumor diameter <5 cm, regardless of age.

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Ethical issues: All authors declare originality and ethical approval of research. Responsibilities of research, responsibilities against local ethics commission are under the authors responsibilities. The study was conducted under defined rules by the local ethics commission guidelines and audits.

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