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MORPHOLOGICAL AND IMMUNOHISTOCHEMICAL FEATURES OF MALIGNANT LIPOMATOUS TUMORS

PhD DISSERTATION ABSTRACT

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2. **Ciongariu AM**, Țăpoi DA, Dumitru AV, Enache V, Marin A, Creangă C, Costache M, *Enhancing Liposarcoma Prognosis - A New Predictive Scoring System Integrating Histopathological Insights; Cancer Management and Research*; IF 3,602 / 2025, Q1, Volumul 17/2025, paginile 331—348; (Capitolele 5, 6)
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INTRODUCTION

The focus of this doctoral research is the identification of histopathological and immunohistochemical features relevant to the prognostic evaluation of malignant lipomatous tumors. Liposarcomas are rare malignant neoplastic proliferations, characterized by significant histomorphological heterogeneity, which entails distinct clinical courses and varied responses to therapy [1].

This study was conducted with the aim of identifying the main clinical, histopathological, and immunohistochemical characteristics with prognostic relevance in liposarcoma. Malignant lipomatous tumors with similar histopathological diagnoses, as classified by the World Health Organization (WHO), may nonetheless exhibit markedly different clinical outcomes in certain patients [2, 3].

The prognosis of patients with malignant lipomatous tumors is typically assessed based on tumor size, mitotic index, and the presence of tumor necrosis—criteria established by the Fédération Nationale des Centres de Lutte Contre le Cancer (FNCLCC) grading system [4]. In prognostic assessment, it is also necessary to consider the histological subtype of the malignant proliferation, given the morphological, immunohistochemical, and molecular biology features specific to each liposarcoma variant [4, 5].

Well-differentiated liposarcoma generally presents a favorable prognosis, despite its association with complex genetic abnormalities [2, 5]. In contrast, dedifferentiated liposarcoma demonstrates a more aggressive clinical course, with a significantly increased risk of progressive disease and lower overall survival rates [2, 5]. Myxoid liposarcoma represents a tumor subtype with a distinct genetic and molecular background compared to other liposarcoma variants [2, 6]. Pleomorphic liposarcoma is a rare malignant lipomatous tumor, with a high potential for local invasion and metastasis. Its prognosis is variable and strongly correlated with tumor localization and TNM stage at diagnosis [7].

Mitotic activity within tumor proliferations is considered a valuable prognostic indicator, as it correlates with recurrence risk and metastatic potential across all anatomical sites of liposarcoma [8]. Another key histopathological element in assessing the malignancy grade and prognosis is tumor necrosis [2]. A retrospective study by Sun et al., conducted on a cohort of 124 patients, demonstrated that tumor necrosis, high mitotic index, and tumor location are independent prognostic factors associated with decreased survival and increased risk of mortality [9].

GENERAL PART – CURRENT STATE OF THE ART

Classification of Malignant Lipomatous Tumors

Liposarcomas are rare malignant mesenchymal neoplasms, accounting for approximately 12.8% of all tumors classified under soft tissue sarcomas [2, 9]. These tumors arise in deep adipose tissue, predominantly affecting the lower limbs and retroperitoneal space, although in rare cases, they may also develop within the adipose tissue of visceral organs [2, 10–12]. There is significant heterogeneity in the histopathological and immunohistochemical profiles of liposarcomas, reflecting underlying genetic and molecular differences [10–12]. Accurate histopathological subtyping of malignant lipomatous tumors is critically important for prognostic evaluation [13].

Well-differentiated liposarcoma / atypical lipomatous tumor are alternative designations for adipocytic neoplasms with low-grade malignancy that occur in specific anatomical locations [14]. The term "atypical lipomatous tumor" is typically reserved for lesions involving superficial or subcutaneous adipose tissue, to highlight their locally invasive potential and to avoid overtreatment with unnecessary oncologic therapies [14, 15].

Myxoid liposarcoma commonly arises in the extremities, trunk, and head and neck regions [2]. It is most frequently associated with the genetic translocation t(12;16)(q13;11), resulting in the FUS-DDIT3 gene fusion [2, 15]. Histopathologically, myxoid liposarcoma is characterized by the presence of atypical lipoblasts embedded in a basophilic, myxoid stroma, along with a distinctive capillary-like vascular pattern [2, 15, 16].

Dedifferentiated liposarcoma is another malignant lipomatous tumor subtype with notable histomorphological and prognostic features [13, 14, 17]. Although it shares a genetic profile similar to well-differentiated liposarcoma, it is associated with a worse prognosis due to both its typical anatomical locations and more aggressive morphology [2, 14]. Dedifferentiated liposarcoma often occurs in the retroperitoneum, mediastinum, or visceral fat [2, 17, 18]. Histologically, it usually demonstrates a well-differentiated lipogenic component with a sudden transition into a high-grade, non-lipogenic sarcoma composed of spindle or rhabdoid cells [10].

Pleomorphic liposarcoma and myxoid pleomorphic liposarcoma are included in a special category of rare tumors with poor clinical outcomes [1, 15, 19]. Pleomorphic

liposarcoma is the rarest type of malignant adipocytic tumor in adults, more frequently arising in the somatic soft tissues of the extremities [15, 19]. Its diagnosis is established histologically in the presence of pleomorphic lipoblasts with multivacuolated cytoplasm, within a background resembling undifferentiated sarcoma [15, 19].

Myxoid pleomorphic liposarcoma, recently described in the literature, is a rare malignant tumor predominantly affecting children and young adults, with a predilection for the mediastinal region [20]. This neoplasm demonstrates clinically aggressive behavior and is frequently associated with postoperative recurrence [20].

Histopathological Prognostic Factors in Malignant Lipomatous Tumors

Dedifferentiated and pleomorphic liposarcomas are considered the malignant lipomatous tumors with the poorest prognosis, being associated with the lowest survival rates and a high risk of disease progression [2, 9, 11]. Although patients with these malignancies are more likely to develop progressive disease and have worse outcomes, current prognostic classification criteria for liposarcomas remain imprecise [2, 9, 11]. This observation stems from the fact that even among patients with the same histological subtype—classified according to WHO guidelines "Tumours of Soft Tissue and Bone," 5th edition—clinical outcomes can vary significantly [2, 15].

Histological Subtype

The histological subtype plays a central prognostic role in malignant lipomatous tumors, given the heterogeneity of this tumor group [2, 15]. Dedifferentiated liposarcoma is a neoplasm with significant metastatic potential [1, 2, 18]. Histologically, it often presents a non-lipogenic tumor component with variable morphology, sometimes showing rhabdomyosarcomatous, chondrosarcomatous, or epithelioid sarcoma differentiation [2, 10]. Another subtype associated with poor prognosis is pleomorphic liposarcoma, a rare malignant proliferation linked to an increased risk of mortality [19].

Mitotic Index

A high mitotic index in patients with liposarcoma has been correlated with poor prognosis in various studies [2, 8, 18]. The FNCLCC grading system for soft tissue sarcomas requires documentation of the mitotic index for all liposarcoma subtypes [8]. In malignant tumors, mitotic activity becomes dysregulated as cancer cells evade normal cell cycle control

mechanisms [18, 21]. Immunohistochemical analysis of Ki-67 expression in liposarcomas is useful for quantifying the mitotic index and assessing the tumor grade [21, 22].

Tumor Necrosis

Tumor necrosis is a key histopathological factor with prognostic relevance in liposarcoma [2, 18]. It is frequently observed in high-grade liposarcomas and has demonstrated statistical significance in predicting patient survival [2, 17]. Some authors have associated tumor necrosis with complex genetic abnormalities, particularly in dedifferentiated and pleomorphic liposarcomas [18, 21, 22].

PERSONAL CONTRIBUTIONS

Working Hypothesis and General Objectives

This doctoral research is based on three retrospective, multicenter studies that analyzed patients diagnosed with malignant lipomatous tumors within the Clinical Pathology Laboratory of the Bucharest University Emergency Hospital and the Pathology Department of the Bucharest Clinical Emergency Hospital, between 2009 and 2023. In total, 99 patients were included in these studies. All patients were followed for at least two years from the time of initial diagnosis or until death, if it occurred earlier.

The working hypothesis underpinning these studies is that liposarcomas represent a heterogeneous group of malignant soft tissue tumors, with clinical evolution and prognosis that vary significantly between patients.

The general objectives of the research were:

- To identify correlations between clinical and histopathological features of malignant lipomatous tumors and their clinical evolution;
- To detect new histopathological factors with predictive value in liposarcomas regarding survival and progressive disease;
- To develop a new scoring system for liposarcomas to improve prognostic and predictive evaluation;
- To assess histopathological and immunohistochemical features of liposarcomas with uncommon localizations.

Doctoral Study 1

This study aimed to identify clinical and histopathological elements with prognostic and predictive value, in relation to the risk of tumor recurrence after surgical excision, disease progression, and death in patients with liposarcoma. A retrospective, multicenter study was conducted including 77 patients diagnosed with primary liposarcoma. Initially, 83 patients were enrolled; however, six were excluded due to incomplete clinical follow-up.

Inclusion criteria:

- Histopathological diagnosis of primary liposarcoma;
- Imaging investigations confirming the presence of secondary lesions following diagnosis;

- Minimum follow-up period of two years, required for assessing progression-free survival (PFS) and overall survival (OS).

Doctoral Study 2

This study involved the development of a risk scoring system applicable to all liposarcoma subtypes, categorizing malignant lipomatous tumors into low-risk and high-risk groups. Risk stratification was based on the likelihood of tumor recurrence after surgical resection, disease progression, and mortality.

The scoring system was created using variables and descriptive statistics from the same cohort of 77 patients with primary liposarcoma, all of whom had a minimum follow-up of two years. Subsequently, an additional 22 patients diagnosed in 2022–2023 were included, yielding a total of 99 cases, all with a two-year follow-up period.

Doctoral Study 3

This study reported a rare case of dedifferentiated myxoid liposarcoma located in the thigh. The rationale for this report lies in the rarity of divergent differentiation in myxoid liposarcoma, as well as the unusual localization of a dedifferentiated liposarcoma in the thigh region. The case involved a 32-year-old male who developed a dedifferentiated liposarcoma in the left lower limb, on a background of a preexisting myxoid liposarcoma.

STUDY OF PROGNOSTIC FACTORS IN MALIGNANT LIPOMATOUS TUMORS

Introduction

The prognosis of patients with malignant lipomatous tumors is evaluated based on tumor size, mitotic index, and presence of tumor necrosis, as stipulated by the FNCLCC grading system [2, 8]. Well-differentiated liposarcomas are generally associated with favorable outcomes, despite their complex genetic abnormalities [2, 14]. In contrast, dedifferentiated liposarcomas are clinically aggressive and associated with an increased risk of progressive disease and reduced survival [2, 10, 15]. Myxoid liposarcomas display distinct genetic and molecular features and are prone to postoperative recurrence and pulmonary metastases [2, 16].

Methodology

A retrospective, multicenter study was performed including 77 patients diagnosed with primary liposarcoma involving somatic soft tissues, internal organs, retroperitoneum, and mediastinum. Cases were sourced from the archives of the Clinical Pathology Laboratory of the Bucharest University Emergency Hospital and the Pathology Department of the Bucharest Clinical Emergency Hospital. The study spanned 13 years (2009–2022).

Inclusion criteria:

- Histopathological diagnosis of primary liposarcoma;
- Imaging evidence of metastases following diagnosis;
- Clinical follow-up of at least 2 years for evaluation of progression-free survival and overall survival.

Main variables:

- Histopathological subtype;
- Mitotic index – number of mitoses/10 high-power fields (HPF);
- Tumor necrosis – absent/present, and estimated percentage;
- Ki-67 proliferation index.

Results

Dedifferentiated and pleomorphic liposarcomas were the most common subtypes among patients with progressive disease and those who died. Fisher's exact test revealed that these subtypes were statistically significant predictors for disease progression (RR=6.625; 95% CI=2.514–17.93; p<0.0001) and death (RR=3.313; 95% CI=1.578–6.964; p=0.0021).

The mean mitotic index for patients with metastases was 8.375/10 HPF (median=5; range: 2–23), whereas for those without metastases it was 3.93/10 HPF (median=2; range: 1–25). A high mitotic index correlated with shorter survival (Mann-Whitney test; p<0.0001). Among survivors, the mean mitotic index was 3.562/10 HPF (median=5; range: 1–25), and the difference was statistically significant for survival (p=0.0011).

Proliferative activity was assessed using two methods:

Manual counting of typical and atypical mitotic figures in HE-stained slides across 10 HPF, following FNCLCC recommendations. Immunohistochemical analysis for Ki-67 nuclear expression, a recognized proliferation marker.

The median Ki-67 index was 4.88% (range: 0.95–24.6%). Among surviving patients, the median Ki-67 index was 1.95% (range: 0.93–22.6%).

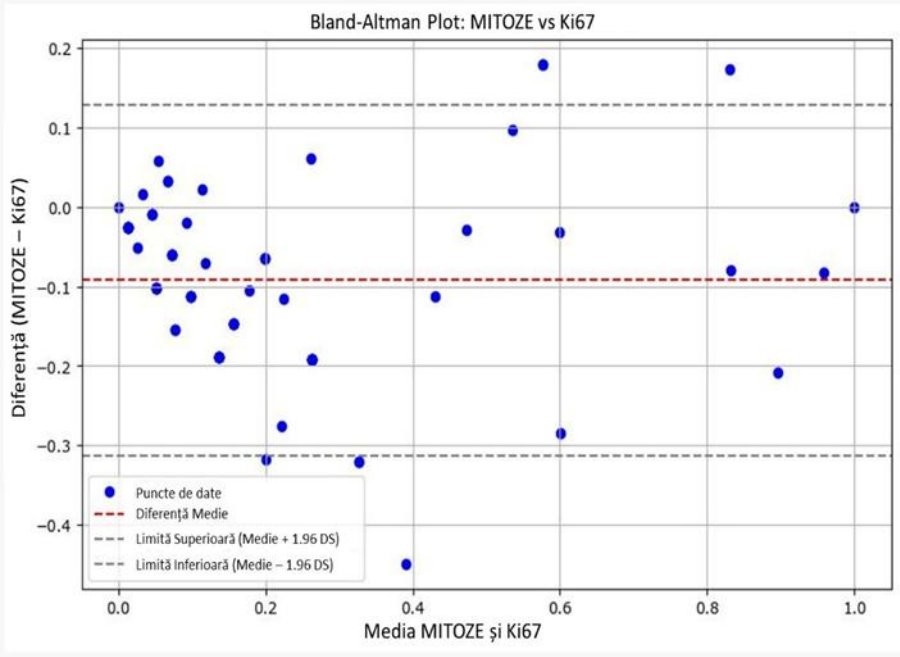

Figure 1 – Bland-Altman analysis comparing Ki-67 values to mitotic count

Tumor necrosis was more frequently observed in patients with metastases. Fisher's exact test confirmed that necrosis was a statistically significant predictor of progressive disease (RR=8.571; 95% CI=1.629–49.89; p=0.007) and lower survival (RR=3.7; 95% CI=1.467–9.919; p=0.0043).

Discussion

The histopathological subtype is a crucial prognostic factor in malignant adipocytic tumors, given the heterogeneity of these neoplasms [23]. According to Fisher's exact test, histologic subtype was a statistically significant predictor of both disease progression and survival. Dedifferentiated liposarcoma demonstrated high metastatic potential, being the most frequent diagnosis among patients with progressive disease. Pleomorphic liposarcoma, associated with high mortality, may also present histological features that complicate differential diagnosis [18, 19].

A high mitotic index was significantly associated with progressive disease and reduced survival during the follow-up period, consistent with FNCLCC guidelines, which recommend mitotic rate assessment as a prognostic parameter for all liposarcoma subtypes [8, 18].

Immunohistochemical analysis of Ki-67 is useful for assessing proliferative activity and tumor grading [22].

Tumor necrosis remains a strong histopathological predictor of poor prognosis in liposarcomas [18, 24]. In this study, necrosis was statistically associated with both progressive disease and reduced survival. Literature data support these findings, indicating that necrosis is frequently present in high-grade liposarcomas and correlates with survival outcomes [18, 25].

DEVELOPMENT OF A NEW ALGORITHM FOR ASSESSING THE RISK OF DISEASE PROGRESSION AND DEATH IN PATIENTS WITH LIPOSARCOMA

Introduction

The second study I conducted aimed to analyze the statistical significance of histopathological characteristics in relation to disease progression and patient survival. We found that the main prognostic indicators for liposarcoma are: histologic subtype, number of mitoses per 10 high-power fields (HPF), and presence of tumor necrosis. Mitotic activity in malignant lipomatous tumors is a well-documented prognostic factor, as reported in the literature and confirmed by our study [15, 25]. Tumor necrosis was also identified as a significant histopathological factor. In this context, the need arose for a new algorithm to classify malignant lipomatous tumors into prognostic-predictive subclasses, allowing for a more detailed assessment of the malignant lesion.

Methodology

The risk score was developed using variables and descriptive statistics obtained from the same multicentric cohort of 77 patients diagnosed between 2009 and 2022. Subsequently, 22 additional patients diagnosed in 2022–2023 were included in the study, all with a 2-year follow-up period. In total, the study included 99 patients, and survival was analyzed in relation to tumor characteristics.

Results

We developed an algorithm called the LEMON score (Liposarcoma Evaluation: Mitosis, Origin, Necrosis), which evaluates three key parameters: histological subtype, mitotic index, and presence of tumor necrosis. The LEMON score classifies liposarcomas into two prognostic categories: low-risk and high-risk lesions.

LEMON Score Evaluation:

Histological subtype:

1 point: well-differentiated liposarcoma

2 points: myxoid liposarcoma

3 points: dedifferentiated or pleomorphic liposarcoma

Mitotic index:

1 point: ≤ 2 mitoses /10 HPF

2 points: 3–4 mitoses /10 HPF

3 points: ≥ 5 mitoses /10 HPF

Tumor necrosis:

1 point: absent

2 points: present

(The thresholds of 2 and 5 mitoses/10 HPF were chosen based on median values in patients without vs. with metastases.)

The total score ranges from 3 to 8:

3–5 points: low-risk category

6–8 points: high-risk category

Based on the LEMON score:

43 patients were classified as low-risk

34 patients as high-risk

Fisher's exact test indicated that tumors classified as high-risk according to the LEMON prognostic-predictive score were significantly associated with progressive disease (RR = 8.853; 95% CI = 2.479–33.52; p = 0.0001).

Fisher’s exact test showed that high-risk tumors were significantly associated with disease progression (RR = 8.853; 95% CI = 2.479–33.52; p = 0.0001) and death (RR = 2.951; 95% CI = 1.321–6.82; p = 0.0091).

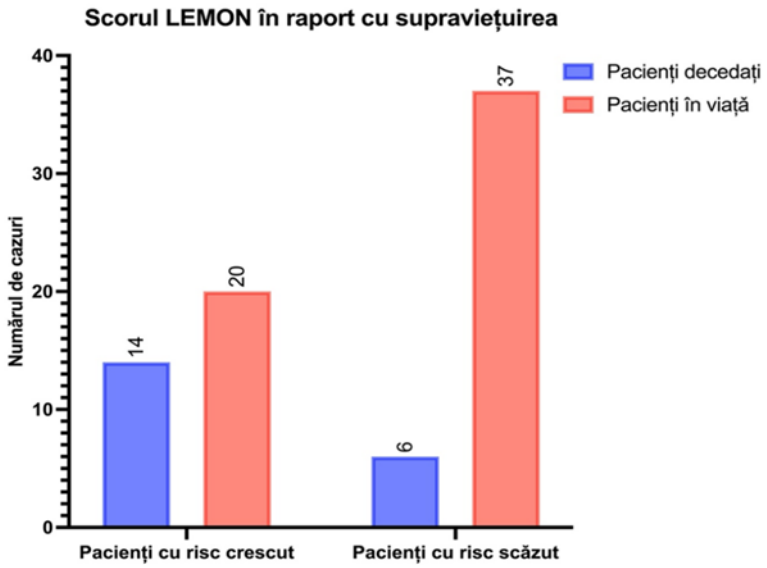

Figure 2 – LEMON score in relation to survival

Survival Analysis

In the next phase of the study, we evaluated the survival outcomes of patients with liposarcoma based on the LEMON score, which incorporates the mitotic index, histological subtype, and tumor necrosis.

Patients with a lower score (3–5), corresponding to the low-risk category, exhibited a stable survival rate over time, maintaining 80% at 5 years.

In contrast, patients classified as high-risk (score 6–8) showed a significant decline, with survival decreasing to 54% at 5 years. The observed difference was statistically significant, with a p-value of 0.0424 – see Figure 3.

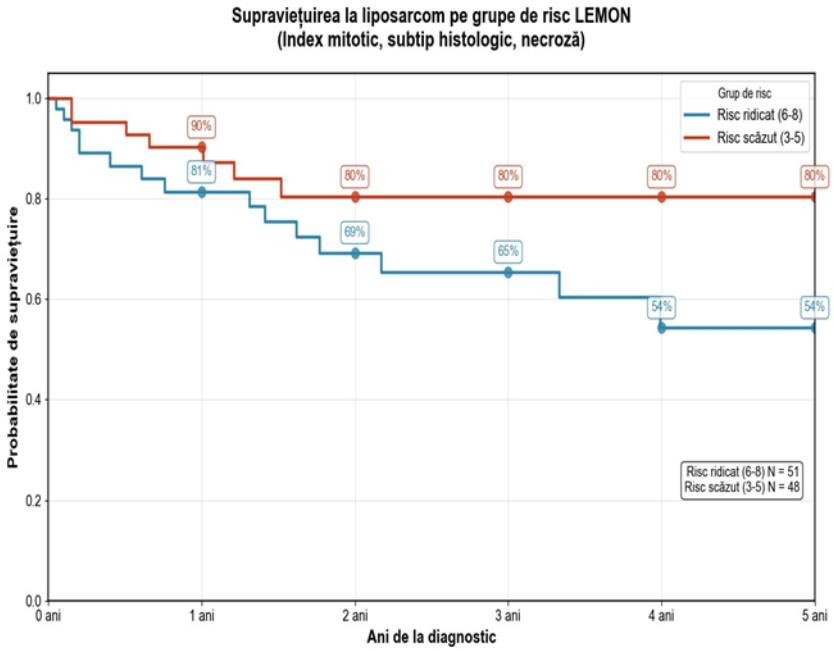

Figure 3 – Survival Outcomes in Patients with Liposarcoma According to the LEMON Score

Kaplan-Meier Curve: One year after diagnosis, the estimated survival rate is 86%, but this decreases to 75% at three years and further declines to 68% at five years, outlining a moderately descending curve – see Figure 4.

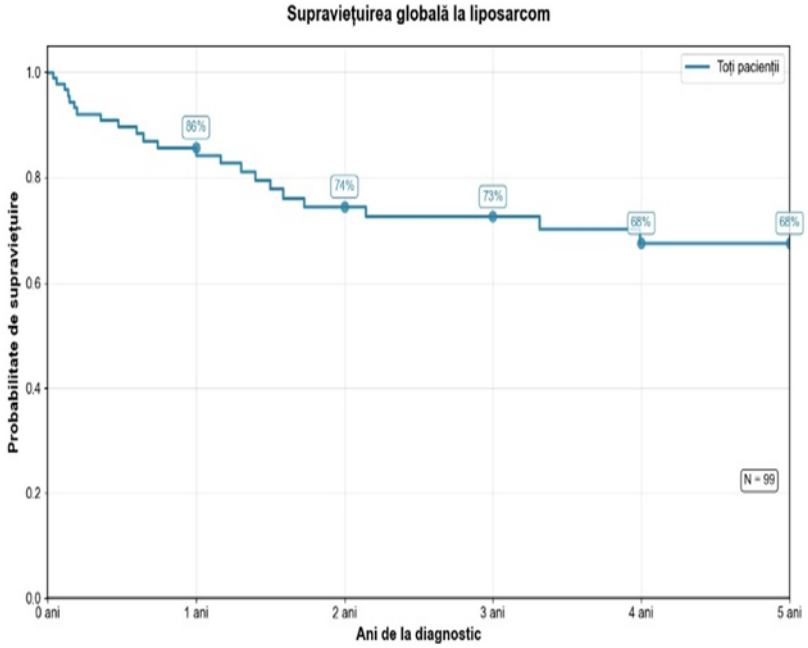

Figure 4 – Kaplan-Meier Analysis of Overall Survival in Patients with Liposarcoma Included in the Study

Most deaths occur within the first two years of follow-up, indicating that this period represents the highest-risk interval for patients.

These findings highlight the importance of close monitoring during the initial years following diagnosis.

Discussion

The results of this study are promising, as the LEMON score can be rapidly assessed during a standard histopathological examination, without incurring additional costs for the patient or the healthcare system. Moreover, the proposed algorithm is easy to apply and does not require extensive experience in soft tissue sarcoma pathology. Despite these clear advantages, the LEMON score should be further evaluated and validated by investigating independent prognostic factors in studies involving larger patient cohorts.

HISTOPATHOLOGICAL AND IMMUNOHISTOCHEMICAL STUDY OF DEDIFFERENTIATED LIPOSARCOMA WITH PECULIAR LOCATION

Dedifferentiated liposarcoma very rarely develops in the somatic soft tissues of the extremities [2, 13]. In the third part of our study, we reported the case of a 32-year-old male who developed dedifferentiated liposarcoma in the thigh region, arising in the context of a pre-existing myxoid liposarcoma.

The expression of MDM2 and CDK4 markers in the cells of the dedifferentiated tumor component confirmed the diagnosis of dedifferentiated liposarcoma originating from a myxoid liposarcoma – see Figure 5.

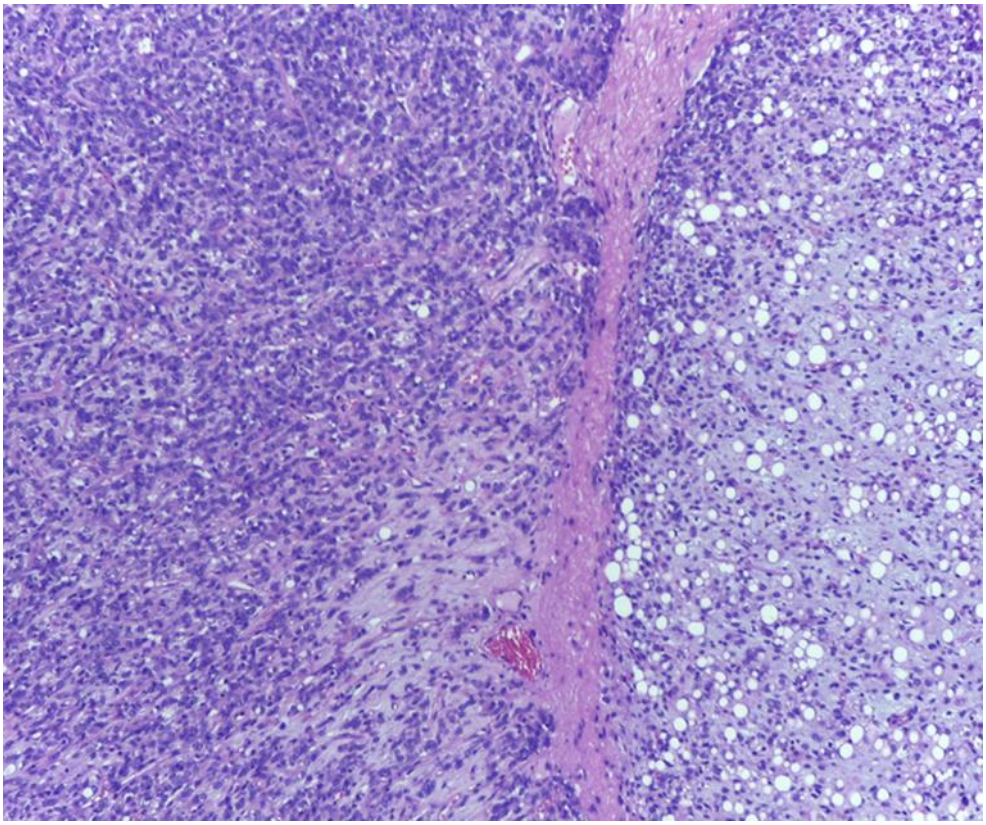

Figure 5 – Dedifferentiated Liposarcoma: A sharp transition is observed between the lipogenic component and the non-lipogenic tumor area, composed of spindle cells exhibiting marked cyto-nuclear atypia; H&E, 100x.

CONCLUSIONS AND PERSONAL CONTRIBUTIONS

The aim of this doctoral research was to identify clinical and histopathological factors with prognostic value in patients diagnosed with malignant lipomatous tumors. The studies we conducted were validated by establishing the prognostic significance of several histopathological parameters used in the assessment of malignant lipomatous tumors: histopathological liposarcoma subtype, number of intratumoral mitoses, and the presence of tumor necrosis. Tumor proliferative activity in liposarcomas was also assessed using immunohistochemical analysis of Ki67 expression as a complementary method, and its sensitivity was compared to that of the mitotic index evaluation on routine H&E-stained slides.

The first retrospective study aimed to identify histopathological indices with prognostic value for estimating the risk of tumor metastasis (progressive disease) and death. We demonstrated that dedifferentiated and pleomorphic liposarcomas are the most aggressive malignant lipomatous tumors, with unfavorable clinical outcomes. Moreover, we showed that the only factors significantly associated with poor prognosis were: histopathological subtype, high mitotic index, and presence of tumor necrosis—both for progression-free survival (PFS) and overall survival (OS).

The second study proposed a novel algorithm for risk assessment in patients diagnosed with liposarcoma. Following the findings of the first study, we identified the need to develop a dedicated risk evaluation system for predicting progression and mortality. The results are relevant, as the LEMON score provides a rapid histopathological assessment method without incurring additional costs. The risk assessment algorithm for progression and death that we proposed is easy to apply and does not require extensive experience in soft tissue pathology. Despite its clear advantages, the LEMON score should be further evaluated in additional studies aiming to investigate prognostic factors in larger patient cohorts.

The third study represents a detailed evaluation of the morphological and immunohistochemical features of dedifferentiated liposarcoma with an unusual localization. This investigation was based on the report of a rare case of dedifferentiated liposarcoma in the lower limb, arising in the context of a pre-existing myxoid liposarcoma. The particularities of this case include the tumor's location in the thigh—a site rarely affected by dedifferentiated liposarcoma, which typically shows a predilection for the retroperitoneum

and mediastinum—and the emergence of the dedifferentiated component from a pre-existing myxoid liposarcoma.

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