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ORIGINAL ARTICLE

Malignant Fibrous Histiocytoma and Undifferentiated Pleomorphic Sarcoma: A Retrospective Single-Center Analysis (1994–2022)

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Abstract

Background: Malignant Fibrous Histiocytoma (MFH), reclassified as undifferentiated pleomorphic sarcoma (UPS) in the 2013 World Health Organization (WHO) classification, is a high-grade pleomorphic sarcoma of mesenchymal origin. It is the most common soft-tissue sarcoma in late adulthood, predominantly affecting males aged 40-80. Surgical resection remains the cornerstone of treatment, while radiotherapy (RT) and chemotherapy (CT) are used selectively to improve local control and survival. This study evaluated the prognostic impact of surgical margin status and adjuvant treatments.

Methods: This retrospective study evaluated 57 patients with MFH/UPS (31 males, 26 females) treated and followed between 1994 and 2022. All patients underwent surgical intervention, and those developing local recurrence were treated with second or third surgical procedures when feasible. Surgical margin status (R0, R1, R2) and its association with local recurrence and distant metastasis were analyzed.

Results: Negative surgical margins (R0 resection) achieved during the initial surgery were strongly associated with improved local disease control. Positive surgical margins (R1/R2) were significantly associated with the development of lung metastases. Repeated surgeries and adjuvant therapies were insufficient to compensate for inadequate initial surgical margins.

Conclusions: Achieving wide, margin-negative resection at the initial surgical intervention is the most critical determinant of oncologic outcome in MFH/UPS. While RT and CT may provide adjunctive benefits in selected cases, optimal surgical management remains the key factor for long-term disease control.

Keywords: Malignant Fibrous Histiocytoma, Undifferentiated Pleomorphic Sarcoma, Soft Tissue Sarcoma, Surgical Margin, Local Recurrence.

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INTRODUCTION

Malignant fibrous histiocytoma (MFH), reclassified as undifferentiated pleomorphic sarcoma (UPS) in the 2013 World Health Organization (WHO) classification, is a high-grade pleomorphic sarcoma of mesenchymal origin.(1) It is the most frequently encountered soft tissue sarcoma in late adulthood; its frequency peaks between the ages of 40 and 80 and its incidence is higher in males.(2) However, the current oncological literature widely refers to this tumor type as undifferentiated pleomorphic sarcoma (UPS) because it does not show recognizable histological differentiation. Despite this change in terminology, UPS corresponds to the former definition of MFH with its high-grade nature and aggressive clinical course, and 5-year overall survival rates are reported to be between 50% and 70%.(3) The lower extremity, especially the thigh, is the most common anatomical site of occurrence.(4) The inflammatory type is generally found in the retroperitoneal region.(5) Approximately 90% of these tumors exhibit deep localization, while subcutaneous involvement is observed in 10% of cases.(6) UPS typically presents as masses of various sizes and follows an aggressive clinical course.(7) Primary treatment remains surgical intervention, which should be comprehensive to ensure excision with negative margins (R0 resection).(8) The effectiveness of adjuvant chemotherapy has been demonstrated, and it is now frequently utilized.(9-10) The most commonly used agents are Ifosfamide and Adriamycin.(11-13) The risk of local recurrence is high, regardless of tumor location, and is primarily related to the adequacy of the surgical procedure.(14,15) Other significant negative prognostic factors include large tumor size (≥ 5 cm), histological Grade 4 classification, extent of necrosis, and retroperitoneal or proximal extremity localization.(16-19)

In this study, we emphasize that surgery must achieve negative surgical margins. If a negative margin cannot be achieved, the procedure must be completed with radical surgery. Otherwise, leaving a positive surgical margin is associated with a substantially elevated risk of local recurrence, although outcomes may vary depending on tumor biology, adjuvant therapy, and patient-specific factors. Additionally, positive surgical margins in these tumors are closely associated with lung metastases. Furthermore, CT and RT have been shown to positively impact patient prognosis.

Therefore, this study aimed to retrospectively evaluate the clinical features, surgical management, and oncological outcomes of patients diagnosed with Malignant Fibrous Histiocytoma/Undifferentiated Pleomorphic Sarcoma treated in our clinic between 1994 and 2022.

MATERIALS AND METHODS

This retrospective study was conducted at the Orthopedics and Traumatology Clinic of the Ministry of Health Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital. A total of 57 patients diagnosed with malignant fibrous histiocytoma (MFH) or undifferentiated pleomorphic sarcoma (UPS) between 1994 and 2022 were included, consisting of 31 males and 26 females. In accordance with the WHO classification updates, cases diagnosed as MFH before 2013 and those diagnosed as UPS after 2013 were included in the study.

Ethical approval for this retrospective study was obtained from the Non-Interventional Clinical Research Ethics Committee of SBÜ Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital (Approval No: 2025-09/132; Date: 02 October 2025). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patients who were surgically treated at our institution for malignant fibrous histiocytoma (MFH) or undifferentiated pleomorphic sarcoma (UPS) between 1994 and 2022 and had available preoperative imaging studies together with complete clinical records were included in the study. Patients with missing imaging data, incomplete medical records, or insufficient follow-up information were excluded from the analysis. Patients presenting with primary metastatic disease at the time of diagnosis were recorded; however, they were excluded from analyses evaluating local recurrence.

Surgical margin status was classified according to standard oncologic definitions used in soft tissue sarcoma surgery. R0 resection was defined as complete tumor excision with histologically negative margins, indicating no microscopic tumor cells at the resection boundary. R1 resection was defined as microscopically positive margins, where tumor cells were identified at the surgical margin on histopathological examination. R2 resection was defined as macroscopically residual tumor remaining after surgery. Surgical margin status

was determined through histopathological evaluation of the resected specimens by experienced musculoskeletal pathologists at our institution, based on routine microscopic examination of the surgical margins.

The indication for neoadjuvant or adjuvant chemotherapy and radiotherapy was determined through a multidisciplinary tumor board evaluation based on tumor size, histological grade, surgical margin status, and evidence of disease progression or recurrence.

All patients underwent initial imaging with direct radiography and PA chest radiography appropriate to the mass localization. MRI was requested for all patients to evaluate soft tissue mass characteristics and stage the tumor. Thoracic CT scans were performed for pulmonary metastasis assessment. Additional imaging included abdominopelvic ultrasonography for inguinal and paraaortic lymphadenopathy in lower extremity cases and axillary ultrasonography for axillary lymphadenopathy in upper extremity cases.

Statistical Analysis

Quantitative variables were analyzed using central tendency and variance measures: mean ± standard deviation. The chi-square test was used to determine differences in proportions or relationships between categorical variables. Statistical significance was set at $p = 0.05$ for all cases. Statistical analyses were performed using IBM SPSS software.

RESULTS

A total of 57 patients diagnosed with MFH or UPS were admitted to our clinic, consisting of 26 females (45.61%) and 31 males (54.39%). The median age of the patients undergoing follow-up and treatment was 56 years (range: 25 - 80) and the mean follow-up period was 5.5 years (range: 3 - 9). Twenty patients (35.09%) presented with metastases, while no metastases were detected in 37 patients (64.91%). The storiform-pleomorphic type was observed in 92.98% of the patients. (Table 1) The most common localization was the lower extremity.

A statistically significant difference was found in the number of operations between Stage IIA and Stage IIB ($p=0.02$) and Stage IIIB ($p=0.028$). A statistically significant difference was observed in the number of operations between Stage IIB and both Stage IIIA ($p=0.027$) and Stage IIIB ($p<0.001$). (Table 2) Recurrence occurred in 19 patients (33.3%) during the 5.5-year follow-up.

Table 3 summarize neoadjuvant and adjuvant treatment strategies as well as the distribution of initial surgical procedures in patients with MFH/UPS. Neoadjuvant chemotherapy and radiotherapy were administered in 28.07% and 12.28% of patients, respectively. Initial surgical management was primarily limb-sparing, with wide resection performed in 50.88% and marginal resection in 33.33% of cases, while amputations and disarticulations were required in a limited number of patients. In contrast to neoadjuvant therapy, adjuvant treatment was more frequently used, with adjuvant chemotherapy administered in 63.16% and adjuvant RT in 33.33% of patients.

Regarding follow-up duration according by pulmonary metastasis status, a total of 20 patients with lung metastases were followed up for a median of 6 years (range 3-9). Patients without lung metastasis (n=37) were followed up for a median of 5 years (range 3-9). There was no significant difference in follow-up duration between patients with lung metastasis and those without ($p=0.845$). (Table 4)

DISCUSSION

Our study highlights the paramount importance of achieving negative surgical margins at the initial operation, as this was strongly associated with improved local control and reduced metastatic risk. Bertoni et al. (5) reported that deep extremity MFH/UPS tumors larger than 5 cm negatively impacted prognosis and recurred within one year. Weiss and Enzinger (7) noted that large and deeply located tumors have a significantly higher likelihood of metastasis. Belal et al. (8) reported that large, high-grade tumors correlated with poor prognosis. In our study, recurrence was seen in 28.6% of T1 tumors and 40.9% of T2 tumors, but no statistically significant difference was found. Furthermore, 56.3% of high-grade tumors developed pulmonary metastasis compared to 34.6% of low-grade tumors, although this difference was not statistically significant. Salo et al. (3) reported that tumors located in the lower extremities had worse prognostic outcomes compared to those in the upper extremities.

Surgical margin status is a critical factor, with R0 (negative) resection being the fundamental goal in STS/UPS

Table 1. Baseline Demographic and Clinical Characteristics of the Study Cohort (N = 57)

Characteristic	Subgroup	Frequency (n)	Percentage (%)
Gender	Female	26	45.6
	Male	31	54.4
Residence	Urban	24	42.1
	Rural	33	57.9
Histological Subtype	Storiform-Pleomorphic	53	93.0
	Myxoid	3	5.3
	Inflammatory	1	1.8
Initial Surgical Procedure	Marginal Resection (MR)	19	33.3
	Wide Resection (WR)	29	50.9
	Above-Knee Amputation (AKA)	3	5.3
	Below-Elbow Amputation (BEA)	1	1.8
	Hip Disarticulation (HD)	4	7.0
	Scapulothoracic Disarticulation (STD)	1	1.8
Pulmonary Metastasis	Present	20	35.1
	Absent	37	64.9

Note: Data are presented as absolute frequencies (n) and relative percentages (%). Abbreviations: MR, Marginal Resection; WR, Wide Resection; AKA, Above-Knee Amputation; BEA, Below-Elbow Amputation; HD, Hip Disarticulation; STD, Scapulothoracic Disarticulation.

Table 2. Distribution of the Number of Surgical Procedures According to Enneking Stage. Values are Presented as Median, Minimum, and Maximum Number of Operations

Stage	Frequency	%	Median	Minimum	Maximum	P
IIA	23	40.35%	1	1	3	0.013
IIB	14	24.56%	2	1	3	-
IIIA	12	21.05%	1	1	3	-
IIIB	8	14.04%	1	1	1	-

Table 3. Distribution of Perioperative Systemic and Radiation Therapies (N = 57)

Therapy Modality	Timing	Administered, n (%)	Not Administered, n (%)
Chemotherapy	Neoadjuvant	16 (28.1)	41 (71.9)
	Adjuvant	36 (63.2)	21 (36.8)
Radiotherapy	Neoadjuvant	7 (12.3)	50 (87.7)
	Adjuvant	19 (33.3)	38 (66.7)

Table 4. Follow-up Periods According to Lung Metastasis

	No Lung Metastasis (n=37)			Lung Metastasis Present (n=20)			P value
	Median	Minimum	Maximum	Median	Minimum	Maximum	
Follow-up Duration	**5**	**3**	**9**	**6**	**3**	**9**	**0.845**

treatment . Shiu et al. (14) reported local recurrence rates of 80–100% after simple biopsy tract excision, which dramatically decreased after local wide excision. Stotter et al. (11) and Lewis et al. (16) emphasized that local recurrence after inadequate surgery (R1/R2) increases the risk of distant metastasis. Karakousis et al. (12) also highlighted the strong correlation between local recurrence and distant metastasis. Wang et al.'s cohort study of 166 UPS patients showed that the R1/R2 resection margin was the sole independent adverse prognostic factor for survival and recurrence.(20,26) Our findings strongly support this, as 19 patients (33.3%) had positive margins, and 13 of the 19 patients initially treated with MR. Pisters et al. suggested that a negative margin distance greater than 1 mm correlates with a reduced risk of local recurrence. (26) Wartenberg et al. suggested that in high-grade STS, a margin greater than 5 mm might be sufficient. (27) Our study supports the literature and shows that surgical excision with wide margins is important.

The impact of adjuvant CT remains controversial. Gherlinzoni et al. and Bacci et al. suggested that neoadjuvant CT helps control microscopic disease and improves prognosis. Standard CT regimens are doxorubicin and/or ifosfamide-based (21,25). Our data showed that 94.4% of patients with metastatic disease received adjuvant CT, compared with 43.2% of patients without metastatic disease. Lee et al. concluded that adjuvant CT may be insufficient to overcome poor prognostic factors. (21) Immunotherapy is a promising development, with UPS showing high PD-L1 expression and favorable responses to agents like Pembrolizumab in trials (23).

Adjuvant RT is a crucial component for local control in high-grade/large tumors (28). Spiro et al. and Reagan et al. showed that RT combined with surgery improves local control.(15,20) Yang et al. found that postoperative RT significantly reduced local recurrence in both low- and high-grade tumors. (17) This is corroborated by Hagemann et al. , who found adjuvant RT to be an independent prognostic factor improving survival in UPS. (28) Our observation that 16 of 19 patients (84.2%) who experienced recurrence received postoperative RT indicates that RT alone may be insufficient to address cases with grossly inadequate surgical margins.

This study has several limitations that should be acknowledged. First, the retrospective design and the relatively limited sample size may restrict the generalizability of the findings. Second, this study represents the

experience of a single institution, which may introduce institutional bias and limit external validity. In addition, the study period spans nearly three decades (1994–2022), during which diagnostic techniques, imaging modalities, pathological classification systems, and treatment strategies for soft tissue sarcomas have evolved, potentially introducing heterogeneity in patient management. More specifically, this temporal heterogeneity reflects several substantive shifts that may have influenced the comparability of cases across the study period. The 2013 WHO reclassification of MFH as undifferentiated pleomorphic sarcoma altered diagnostic criteria, and earlier cases originally diagnosed as MFH might be reclassified differently with current immunohistochemical and molecular techniques. (29) Imaging modalities such as MRI and thoracic CT, as well as PET-CT for staging and surveillance, became increasingly available and refined throughout this interval, which may have affected both the detection of local extent and the identification of pulmonary metastases. (30) Surgical philosophy also evolved, with a progressive shift toward limb-sparing wide resections and greater emphasis on negative-margin oncologic surgery. (15) Adjuvant treatment protocols have likewise changed, including the broader use of doxorubicin/ifosfamide-based regimens, modern radiotherapy techniques such as IMRT and image-guided radiotherapy, (31) and, more recently, the emergence of immunotherapeutic approaches. (32) Although a multidisciplinary tumor board guided treatment decisions throughout the study period, these temporal changes were not formally analyzed as covariates, and we did not perform stratified analyses by treatment era. Therefore, the influence of practice evolution on outcomes cannot be excluded, and our findings should be interpreted with this temporal heterogeneity in mind. Although the follow-up duration allowed the evaluation of local recurrence and pulmonary metastasis, comprehensive survival analyses such as overall survival, disease-free survival, and metastasis-free survival using Kaplan–Meier methods were not performed. Furthermore, due to the sample size and retrospective nature of the dataset, multivariate analyses to determine independent prognostic factors could not be conducted. In addition, the statistical analysis was largely descriptive and limited to χ^2 testing, without multivariate modeling or time-to-event analyses; this relatively basic approach may not fully support causal inferences regarding the prognostic role of surgical margins and adjuvant therapies, and the present findings should therefore be regarded as hypothesis-generating rather than confirmatory. Therefore, larger multi-center prospective studies are required to better clarify the independent prognostic role of surgical margin status and adjuvant therapies in patients with MFH/UPS.

This study demonstrated that achieving negative surgical margins (R0 resection) is the primary and most critical prognostic factor in the treatment of MFH/UPS. If a negative margin (R1/R2 resection) cannot be achieved, radical surgery must be performed. In our cohort, positive surgical margins were strongly associated with local recurrence and are closely associated with pulmonary metastasis. Our findings suggest that CT contributes to microscopic disease control and positively impacts prognosis. Postoperative RT may contribute to local control and is recommended as an adjunct in selected cases; however, in our cohort RT alone did not appear sufficient to compensate for grossly inadequate surgical margins, underscoring that adjuvant therapy cannot substitute for adequate primary resection. Taken together, these findings reinforce that meticulous surgical planning aimed at achieving wide, margin-negative resection at the initial intervention remains the cornerstone of optimal oncologic outcomes in MFH/UPS, and should be prioritized within a multidisciplinary treatment framework.

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Abbreviations List

MFH: Malignant Fibrous Histiocytoma
UPS: Undifferentiated Pleomorphic Sarcoma
STS: Soft Tissue Sarcoma
WHO: World Health Organization
R0: Microscopically negative surgical margin
R1: Microscopically positive surgical margin
R2: Macroscopically positive surgical margin

CT: Chemotherapy
RT: Radiotherapy
MRI: Magnetic Resonance Imaging
PET-CT: Positron Emission Tomography-Computed Tomography
IMRT: Intensity-Modulated Radiation Therapy
IGRT: Image-Guided Radiation Therapy
MR: Marginal Resection
WR: Wide Resection
AKA: Above-Knee Amputation
BEA: Below-Elbow Amputation
HD: Hip Disarticulation
STD: Scapulothoracic Disarticulation
PD-L1: Programmed Death-Ligand 1
SPSS: Statistical Package for the Social Sciences.

Ethics Approval and Consent to Participate

Ethical approval for this retrospective study was obtained from the Non-Interventional Clinical Research Ethics Committee of SBÜ Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital (Approval No: 2025-09/132; Date: 02 October 2025). The study was conducted in accordance with the principles of the Declaration of Helsinki. Given the retrospective nature of the analysis and the use of de-identified archival data, the requirement for individual written informed consent was waived by the Ethics Committee.

Consent for Publication

Not applicable. The manuscript does not contain any individual person's identifying data, images, or videos.

Availability of Data and Materials

The datasets generated and/or analysed during the current study are not publicly available due to institutional data-protection policies regarding patient records, but are available from the corresponding author on reasonable request and after appropriate institutional approval.

Competing Interests

The authors declare that they have no competing interests.

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Authors Contributions

Idea/Concept: MAB, BA. Desıgn: MAB, BA. Control/Supervısıon MAB, BA. Data Collectıon And/Or Processıng: MAB, BA. Analysıs And/Or Interpretatıon: MAB, BA. Lıterature Revıew: MAB, BA. Wrıtıng The Artıcle: MAB, BA. Crıtıcal Revıew: MAB, BA. References And Fundıngs: MAB, BA. Materıals: MAB, BA. Other: MAB, BA.

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