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Predicting the Prognosis of Undifferentiated Pleomorphic Soft Tissue Sarcoma.

A 20-year Experience of 266 Cases

Running Head: UPS Prognostic Factors

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Abstract

Background

Undifferentiated pleomorphic sarcoma (UPS) is a rare malignant tumour of mesenchymal origin, which was conceived following re-classification of malignant fibrous histiocytoma (MFH). The objective of this study is to determine prognostic factors for the outcome of UPS, following multi-modal treatment.

Methods

Data of UPS tumours from 1996 to 2016 was collected, totalling 266 unique UPS patients. Median follow-up was 7.8 years. All tumours were retrospectively analysed for prognostic factors of the disease, including local recurrence (LR) and metastatic disease (MD) at diagnosis, tumour size, ~~grade,~~ location and depth, patient age, adjuvant therapy, and surgical margin. Overall survival (OS), post-treatment local recurrence and metastatic-free survival were assessed as outcomes.

Results

The 5- and 10-year OS rates for all ages were 60% and 48%, respectively, with a median survival time of 10.1 years. Multivariate analysis revealed that the adverse prognostic factors associated with decreased OS were older age ($p<0.001$;Hazard Ratio,1.03) and MD at diagnosis ($p=0.001$; 2.89), with upper extremity tumours being favourable ($p=0.043$; 2.30). Poor prognosis for post-operative LR was associated with older age ($p=0.046$; 1.03) and

positive surgical margins (p=0.028; 2.68). Increased post-treatment MD was seen in patients with large tumours (5-9cm [p<0.001; 4.42], ≥10cm [p<0.001; 6.80]) and MD at diagnosis (p<0.001; 3.99), adjuvant therapy was favourable, shown to reduce MD (p<0.001; 0.34).

Conclusions

UPS is a high-grade STS, for which surgery striving for negative margins, with radiotherapy, is the treatment of choice. Older age, lower extremity location, MD at presentation, large size and positive surgical margins, were unfavourable.

Introduction

Soft tissue sarcomas (STS) are heterogeneous and rare tumours showing mesenchymal differentiation, accounting for less than 1% of all malignant neoplasms and includes more than 60 different histologic subtypes[1]. One such subtype, undifferentiated pleomorphic sarcomas (UPS), are tumours formerly known as malignant fibrous histiocytoma (MFH), which was first described in 1963[2]. It was previously deemed a distinct tumour type derived from histiocytes, and represented the most common type of STS in adults[3]. Despite MFH's long history, the World Health Organization classifications of STS consider the term a misnomer, as it encompasses the morphologic manifestations of a variety of poorly differentiated tumours[4,5]. Approximately 30–50% of all UPS patients die within 5 years of initial diagnosis. Despite surgically-achieved local control of the primary tumour, 40% of patients with these high-grade tumours develop pulmonary metastases. The median survival from the diagnosis of metastatic disease is reported to be 8–12 months[6].

The current mainstay of treatment for STS is surgical wide-resection with adjuvant radiotherapy[7-9]. Numerous studies have analysed the prognostic factors of MFH[10-18], however, only one study has explicitly studied prognostic factors of the reclassified UPS subtype[19]. Hence, we sought to determine which clinicopathologic factors correlate with changes in overall survival, metastatic-free survival and local recurrence-free survival, in a bid to improve diagnostic capabilities within the musculoskeletal oncology community. This study is the largest of its kind.

Methods

This study was designed as a retrospective analysis at a single institute and was ethics review board approved (Ethics number: QA 054/16).

Patients

From 1996 to 2016, 274 undifferentiated pleomorphic sarcomas were treated at our institution and recorded in a prospective database. St. Vincent's Hospital, Melbourne, is a tertiary referral sarcoma centre, with a catchment area of 6.3 million people. All tumours were classified by a specialist sarcoma pathologist. The clinicopathologic and treatment characteristics of our cohort are outlined in Table 1.

Treatment

All 266 patients referred to our centre underwent surgical excision at our institution, including all those presenting with prior excision. Adjuvant radiotherapy was administered to 91% and adjuvant chemotherapy to 3% of our patients. Neo-adjuvant therapy was not administered.

Surgical margins were classified according to Enneking staging (intralesional, marginal, wide, radical). Intralesional and marginal margins are classified as inadequate. Wide and radical margins are classified as adequate. If radiotherapy was performed in conjunction with marginal margins, the margin was classified as adequate.

Prognostic Factors and Outcome Measures

Tumour-related factors including gender, age, depth (in relation to the deep fascia), size, location and distant metastases ~~and histological grade according to the Federation Nationale des Centres de Lutte Contre le Cancer (FNCLCC) grading system~~ were collected from patient records. Treatment-related factors including adjuvant therapy, surgery prior to referral and its associated margins. Overall and disease-specific survival, local recurrence and metastatic disease were used as outcome measures.

Results

Disease outcome and patient survival

Median follow-up for patients was 85 months. At the time of final follow-up, the overall survival rate was 56%. Amongst those who had died, 72% had died of disease. A total of 7% of surviving patients were alive with disease at final follow-up. Post-treatment local recurrence was observed in 15% of patients and metastatic disease in 38%. The 5-year overall survival, metastatic-free survival and local recurrence-free survival were 60%, 62% and 85%, respectively.

Overall Survival

Univariate analysis revealed that older age, presence of metastases at diagnosis, adjuvant therapy, tumour depth and size were significant prognostic factors for patient overall survival (Table 2).

The 5- and 10-year OS rates (all ages) were 60% and 48%, respectively, with a median survival time of 10.1 years. Patients aged ≥ 70 years had a 1.81 times greater risk of death than those < 70 years. LR at the time of presentation, following pre-referral surgery, lead to a 12% increased risk of death. Radiotherapy had a positive effect on patient survival, with a 68% reduction in mortality. Tumours sized 5-9cm and ≥ 10cm having a 108% and 268% greater risk of mortality, respectively, than those < 5cm. Metastatic disease at the time of presentation also had a significant impact on survival, with a 456% increase in mortality, compared to those presenting metastasis-free.

Inadequate margins were associated with 1.82 times the rate of death relative to wide margins. Furthermore, radical margins were associated with 3.59 times the rate of death relative to wide margin. This was supported by multivariate analysis revealing radical margins were associated with 2.89 times the rate of death relative to wide margins. The predominant theory behind this is that patients undergoing radical margins had an average tumour size of 12.40cm, which has a direct statistical correlation with increased rate of death.

Local Recurrence

Patient age, local recurrence (LR) at diagnosis and surgical margin were all found to be significant prognostic factors, on univariate analysis, for developing LR after definitive surgery at our institution (Table 3).

The 5-year and 10-year OS rates for patients ≥ 70 years were 77.4% and 71.9%, respectively, and 88.4% and 83.3%, for those < 70 years. LR at the time of presentation, following pre-referral surgery, showed a higher rate of post-treatment LR at 5-years, with 21.7% of those with a history of LR and only 14.2% of those with no prior LR. Patients who had inadequate surgical margins had a 2.75 times increased risk of developing LR, when compared to patients with adequate margins.

Multivariate analysis revealed age and surgical margins to be significant factors when predicting LR post-op. Every 1 year older at diagnosis associated with 1.03 times the rate of death. Inadequate surgical margin saw a 2.68 fold increase in the rate of LR, when compared to adequate surgical margins.

Metastatic Disease

Univariate analysis revealed that gender, presence of metastases at diagnosis, adjuvant therapy, tumour depth and size were significant prognostic factors for patients developing metastatic disease after definitive surgery (Table 4).

A history of metastatic disease at the time of initial diagnosis was significantly associated with a 3.51 fold increase in the development of post-surgical metastatic disease. Tumours located deep to the muscle fascia showed a 93% increased risk of developing metastatic disease. Adjuvant therapy saw a 66% reduction in metastatic disease. Tumour size was the most powerful adverse prognostic factor in determining the risk of developing metastatic disease, on univariate analysis. Tumours which were 5-9cm had a 4.34 fold greater risk of death than those < 5cm, and those ≥ 10cm had a 7.50 fold greater risk of mortality than those

< 5cm. The difference in 5-year metastatic rates between the groups < 5cm, 5-9cm and ≥ 10cm, were 11.2%, 40.5% and 54.1%, respectively.

Metastatic disease at diagnosis, adjuvant therapy and size were significant on multivariate analysis for predicting post treatment metastases (Table 5). Tumours sized 5-9cm and ≥10cm had a 4.42 and 6.80 fold increased risk, respectively, of developing metastatic disease, when compared to tumours <5cm.

Discussion

The former classification of MFH consisted of a wide range of histological appearances[4]. The term 'MFH' is now a misnomer as advances in histopathology and cytogenetic testing have shown no evidence of true histiocytic differentiation, meaning it encompasses the morphologic manifestations of a variety of poorly differentiated tumours rather than being a single entity[20, 21]. Gene sequencing studies have recently confirmed this conceptual shift[22-24]. MFH was previously the most common STS in adults, accounting for 50% of diagnoses. Since the reclassification UPS accounts for only 5% of adult STS[21].

Radiotherapy has a well-established role in the treatment regimen of both localised and metastatic STS. The principal purpose of radiotherapy is to inactivate the microscopic extensions of tumour, surrounding the tumour capsule, reducing surgical potential for seeding and histologically positive margins, subsequently lowering the rate of LR. LR rates as high as 30% were reported prior to the use of radiotherapy, with a reduction to 15% once radiotherapy and surgery were combined[7].

The 66% reduction in metastatic disease with the use of adjuvant radiotherapy in our cohort, is supported by randomised control trials which have confirmed that surgery combined with radiotherapy is the most effective management for localised high-grade STS[25].

Our findings revealed a trend toward poorer overall survival for inadequate margins and inadequate margins leading to a significantly higher rates of LR. Lehnhardt's UPS study revealed negative margin tumours have a 5-year OS of 79%, positive margins 23% and intralesional having 0%[19].

Large tumour size is the most widely reported negative prognostic factor for UPS and MFH tumours[10,12,14,16-19]. The most powerful multivariate finding in our study was the 580% increase in the risk of metastatic disease for tumours ≥ 10cm, when compared to smaller (0-4cm) lesions. Zagar et al's analysis of 271 MFH tumours similarly revealed a significant increase in metastatic disease risk, with a near-double risk when comparing tumours < 10cm and ≥ 10cm.

A primary theory behind this is that larger tumours have cycled through more rounds of cell division than smaller tumours, allowing for greater outgrowth of variants which are able to metastasise[16]. Additionally, their larger size may allow them to cross fascial planes and spread to other tissues, leading to disease that is harder to control. Larger tumours may have grown to a particular size due to more aggressive tumour biology, related to intrinsic tumour characteristics, such as cell cycle dysregulation or tumour angiogenesis.

Our findings of increased mortality and metastatic disease for deep-seated tumours is likely due to deeper tumours being less palpable and visible in the early stages of disease. Salo *et*

al's cohort of MFH tumours showed superficial tumours were associated with improved disease-specific survival[16]. Similarly, a possible cause for lower-extremity tumours having poorer survival, compared to upper-extremity, is due to lower extremities having larger soft tissue mass, with deeper sites to originate, allowing the tumour to increase in size prior to detection.

~~The significantly higher rates of LR and mortality in patients who presented to our centre after excision elsewhere, reinforces the importance of sarcoma specialist centre management over non-sarcoma centre care.~~ Although not supported by data in our patient cohort, referral to a sarcoma centre is still advised. Targeted, centralised and up to date care is provided in a setting where each case is reviewed by a dedicated sarcoma multi-disciplinary team.

Our study showed that LR may occur in the presence or the absence of metastases, meaning the presence alone of the LR is not an accurate predictor of metastases. There is some conjecture with these findings, as studies have shown that the timing of LR to be predictive of metastatic disease[19]. If LR occurs in the presence of metastatic disease, it likely reflects the local manifestations of a systemically aggressive tumour.

Conclusion

UPS is a rare, high-grade, STS manifesting itself in a variety of histologic appearances. It was conceived as a distinct entity from the former broad category of MFH, which encompassed multiple histological subtypes. This evolution in pleomorphic STS classification is representative of how surgical pathology has progressed over the past three decades.

Adverse prognostic factors for UPS tumours include large size, deep-seated location, positive surgical margins, lower-extremity location, local recurrence and metastases at presentation. Adjuvant radiotherapy has been shown to reduce both mortality and metastatic spread of disease.

Disclosure Statement

- No public or private funding was supplied in the undertaking of this study
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- No conflicts of interest are associated with the undertaking of this study
- Preliminary data from this study was presented at the 2017 Australian Orthopaedic Association's Annual Scientific Meeting in Adelaide, South Australia

References

1. Singer S, Demetri GD, Baldini EH, Fletcher CD. Management of soft-tissue sarcomas: an overview and update. The Lancet Oncology. 2000;1:75-85.

2. Ozzello L, Stout AP, Murray MR. Cultural characteristics of malignant histiocytomas and fibrous xanthomas. Cancer. 1963;16:331-44.

3. Weiss SW, Enzinger FM. Malignant fibrous histiocytoma. An Analysis of 200 Cases. Cancer. 1978;41(6):2250-66.

4. Fletcher CD, Unni KK, Mertens F. Pathology and Genetics of Tumours of Soft Tissues and Bone. WHO Classification of Tumours. 3rd ed. Lyon, France:IARC Press;2002.

5. Fletcher CD, Bridge JA, Hogendoorn PCW, Mertens F. WHO Classification of Tumours of Soft Tissue and Bone. 4th Edition ed. Lyon, France:IARC Press;2013.

6. Weitz J, Antonescu CR, Brennan MF. Localized extremity soft tissue sarcoma: improved knowledge with unchanged survival over time. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2003;21(14):2719-25.

7. O'Connor MI, Pritchard DJ, Gunderson LL. Integration of limb-sparing surgery, brachytherapy, and external-beam irradiation in the treatment of soft-tissue sarcomas. Clinical Orthopaedics and Related Research. 1993(289):73-80.

8. O'Sullivan B, Davis AM, Turcotte R, Bell R, Catton C, Chabot P, et al. Preoperative versus postoperative radiotherapy in soft-tissue sarcoma of the limbs: a randomised trial. Lancet. 2002;359(9325):2235-41.

9. Davis AM, O'Sullivan B, Turcotte R, Bell R, Catton C, Chabot P, et al. Late radiation morbidity following randomization to preoperative versus postoperative radiotherapy in extremity soft tissue sarcoma. Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology. 2005;75(1):48-53.

10. Belal A, Kandil A, Allam A, Khafaga Y, El-Husseiny G, El-Enbaby A, et al. Malignant fibrous histiocytoma: a retrospective study of 109 cases. American journal of clinical oncology. 2002;25(1):16-22.

11. Fletcher CD, Gustafson P, Rydholm A, Willen H, Akerman M. Clinicopathologic re-evaluation of 100 malignant fibrous histiocytomas: prognostic relevance of subclassification. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2001;19(12):3045-50.

12. Gibbs JF, Huang PP, Lee RJ, McGrath B, Brooks J, McKinley B, et al. Malignant fibrous histiocytoma: an institutional review. Cancer investigation. 2001;19(1):23-7.

13. Hsu HC, Huang EY, Wang CJ. Treatment results and prognostic factors in patients with malignant fibrous histiocytoma. Acta oncologica (Stockholm, Sweden). 2004;43(6):530-5.

14. Le Doussal V, Coindre JM, Leroux A, Hacene K, Terrier P, Bui NB, et al. Prognostic factors for patients with localized primary malignant fibrous histiocytoma: a multicenter study of 216 patients with multivariate analysis. Cancer. 1996;77(9):1823-30.

15. Pezzi CM, Rawlings MS, Jr., Esgro JJ, Pollock RE, Romsdahl MM. Prognostic factors in 227 patients with malignant fibrous histiocytoma. Cancer. 1992;69(8):2098-103.

16. Salo JC, Lewis JJ, Woodruff JM, Leung DH, Brennan MF. Malignant fibrous histiocytoma of the extremity. Cancer. 1999;85(8):1765-72.

17. Vasileios KA, Eward WC, Brigman BE. Surgical treatment and prognosis in patients with high-grade soft tissue malignant fibrous histiocytoma of the extremities. Archives of orthopaedic and trauma surgery. 2012;132(7):955-61.

18. Zagars GK, Mullen JR, Pollack A. Malignant fibrous histiocytoma: outcome and prognostic factors following conservation surgery and radiotherapy. International journal of radiation oncology, biology, physics. 1996;34(5):983-94.

19. Lehnhardt M, Daigeler A, Homann HH, Schwaiberger V, Goertz O, Kuhnen C, et al. MFH revisited: outcome after surgical treatment of undifferentiated pleomorphic or not

otherwise specified (NOS) sarcomas of the extremities -- an analysis of 140 patients. Langenbeck's archives of surgery. 2009;394(2):313-20.

20. Fletcher CD. The evolving classification of soft tissue tumours: an update based on the new WHO classification. Histopathology. 2006;48(1):3-12.

21. Randall RL, Albritton KH, Ferney BJ, Layfield L. Malignant fibrous histiocytoma of soft tissue: an abandoned diagnosis. American journal of orthopedics (Belle Mead, NJ). 2004;33(12):602-8.

22. Lee YF, John M, Edwards S, Clark J, Flohr P, Maillard K, et al. Molecular classification of synovial sarcomas, leiomyosarcomas and malignant fibrous histiocytomas by gene expression profiling. Br J Cancer. 2003;88(4):510-5.

23. Nakayama R, Nemoto T, Takahashi H, Ohta T, Kawai A, Seki K, et al. Gene expression analysis of soft tissue sarcomas: characterization and reclassification of malignant fibrous histiocytoma. Modern pathology : an official journal of the United States and Canadian Academy of Pathology, Inc. 2007;20(7):749-59.

24. Nielsen TO, West RB, Linn SC, Alter O, Knowling MA, O'Connell JX, et al. Molecular characterisation of soft tissue tumours: a gene expression study. Lancet. 2002;359(9314):1301-7.

25. Rosenberg SA, Tepper J, Glatstein E, Costa J, Baker A, Brennan M, et al. The treatment of soft-tissue sarcomas of the extremities: prospective randomized evaluations of (1) limb-sparing surgery plus radiation therapy compared with amputation and (2) the role of adjuvant chemotherapy. Ann Surg. 1982;196(3):305-15.

Appendix

Table 1: Clinicopathologic and Treatment Characteristics of 266 patients with undifferentiated pleomorphic sarcoma.

Variables	Overall n (%)
Sex	
- **Male**	144 (54%)
- **Female**	122 (46%)
Age	
- **Median**	63.8
- **Standard Deviation**	± 14.4
- **Range**	19 - 94
Depth	
- **Deep**	215 (80.8%)
- **Superficial**	51 (19.2%)
Size	
- **0-4cm**	66 (24.8%)
- **5-9cm**	100 (37.6%)
- **≥10cm**	100 (37.6%)
- **Average**	8.8cm
- **Standard Deviation**	± 6.6cm
- **Range**	1 – 55cm
Location	
- **Upper Extremity**	64 (24.1%)
- **Lower Extremity**	179 (67.3%)
- **Trunk**	23 (8.6%)
Surgery Prior to Referral	
- **Prior Surgery**	96 (36.1%)
- **No Surgery**	170 (63.9%)
Margins upon referral	
- **Adequate**	10 (10.4%)
- **Inadequate**	86 (89.6%)
Post-treatment Margin	
- **Adequate**	248 (93.2%)
Wide	226
Radical	22
- **Inadequate**	18 (6.8%)
Marginal	13
Intralesional	5
Limb-Sparing Surgery	
- **Limb-sparing**	242 (91.0%)
- **Major Amputation**	24 (9.0%)
Metastases at Diagnosis	
- **Metastases**	17 (6.39%)
- **No Metastases**	249 (93.61%)
Local Recurrence at diagnosis	
- **Recurrence**	51 (19.2%)
- **No Recurrence**	215 (80.8%)

Adjuvant Therapy	
- **Chemotherapy**	1 (0.38%)
- **Radiotherapy**	237 (89.1%)
- **Combined**	6 (2.3%)
- **Nil**	22 (8.27%)
Post Treatment Local Recurrence	
- **Recurrence**	40 (15.0%)
- **No Recurrence**	226 (85.0%)
Post Treatment Metastases	
- **Metastases**	100 (37.6%)
- **No Metastases**	166 (62.4%)

Table 2: Univariate analysis of prognostic factors for overall survival in 266 Undifferentiated Pleomorphic Sarcoma patients

Variable	No. of patients	Death HR (95%CI)	p value	5-year OS % (95%CI)	p value	10-year OS % (95%CI)	p value
Age							
- **70 years and older**	101	1.81 (1.39-2.35)	<0.001*	46.4 (35.7-56.4)	0.004*	31.5 (20.4-43.1)	0.0084*
- **Under 70 years**	165	1.00		68.0 (60.0-75.0)		60.3 (51.0-68.4)	
Gender							
- **Male**	144	1.30 (0.90-1.88)	0.164	58.4 (49.3-66.3)	0.0846	46.0 (36.4-55.1)	0.1629
- **Female**	122	1.00		61.4 (51.2-70.1)		54.3 (43.0-64.3)	
Local Recurrence at diagnosis							
- **Recurrence**	51	1.00		59.1 (44.0-71.4)	0.5166	52.2 (36.2-66.1)	0.5894
- **No recurrence**	215	0.88 (0.55-1.39)	0.575	59.6 (52.0-66.4)		48.1 (39.8-56.0)	
Metastases at diagnosis							
- **Metastases**	17	5.56 (3.23-9.57)	<0.001*	Insufficient numbers	N/A	Insufficient numbers	N/A
- **No metastases**	249	1.00		63.9 (57.1-69.9)		52.9 (45.2-60.0)	
Adjuvant Therapy							
- **Adjuvant Therapy**	244	0.32 (0.19-0.54)	<0.001*	63.4 (56.6-69.5)	0.0068*	53.2 (45.5-60.3)	<0.0011*
- **No Adjuvant**	22	1.00		16.2 (3.0-38.7)		8.1 (0.1-29.6)	
Pre-referral surgery							
- **Prior surgery**	96	0.74 (0.50-1.09)	0.132	61.7 (50.4-71.2)	0.8128	53.5 (41.1-64.5)	0.2955
- **No prior surgery**	170	1.00		58.7 (50.3-66.2)		47.1 (37.9-55.8)	
Location							
- **Upper extremity**	64	0.66 (0.41-1.07)	0.092	67.7 (53.2-78.5)	0.1114	57.3 (40.8-78.5)	0.1364
- **Lower extremity**	179	1.00		57.3 (49.2-64.6)		45.7 (37.0-54.1)	
- **Trunk**	23	0.59 (0.29-	0.155	59.9 (35.2-77.7)		59.9 (35.2-77.7)	

		1.22)					
Depth - **Deep** - **Superficial**	215 51	1.73 (1.05-2.84) 1.00	0.030*	57.1 (49.6-63.9) 70.8 (55.6-81.6)	0.7098	45.4 (36.9-53.6) 63.6 (48.0-75.7)	0.2072
Size - **0-4cm** - **5-9cm** - **≥10cm**	66 100 100	1.00 2.08 (1.17-3.68) 3.37 (1.93-5.87)	 0.012* <0.001*	78.3 (64.6-87.1) 60.7 (49.5-70.1) 47.2 (36.5-57.1)	<0.0013*	72.5 (57.2-83.0) 50.0 (37.3-60.6) 35.3 (24.6-46.3)	<0.0011*
Margin - **Adequate** - **Inadequate**	248 18	1.00 1.57 (0.88-2.80)	 0.123	60.9 (54.0-67.1) 45.6 (22.5-66.1)	0.3622	51.8 (44.1-58.9) 27.4 (9.4-49.1)	0.0748

OS- Overall Survival
*Statistically significant

Table 3: Univariate analysis of prognostic factors for local recurrence in 266 Undifferentiated Pleomorphic Sarcoma patients

Variable	No. of patients	LR HR (95%CI)	p value	5-year LRFS % (95%CI)	p value	10-year LRFS % (95%CI)	p value
Age - **70 years and older** - **Under 70 years**	101 165	1.63 (0.93-2.88) 1.00	0.090	77.4 (65.7-85.5) 88.4 (81.2-92.9)	0.034*	71.9 (58.1-81.8) 83.3 (73.7-89.7)	0.0413*
Gender - **Male** - **Female**	144 122	0.81 (0.42-1.55) 1.00	0.531	84.8 (76.0-90.5) 84.2 (75.1-90.1)	0.6611	81.5 (71.6-88.2) 76.5 (63.5-85.3)	0.7631
Local Recurrence at diagnosis - **Recurrence** - **No recurrence**	51 215	1.51 (0.73-3.12) 1.00	0.269	78.3 (62.1-88.2) 85.8 (79.1-90.5)	0.0336*	74.4 (56.8-85.6) 80.1 (71.1-86.6)	0.2128
Metastases at diagnosis - **Metastases** - **No metastases**	17 249	2.99 (0.90-9.91) 1.00	0.074	Insufficient numbers 85.2 (79.2-89.5)	N/A	Insufficient numbers 79.8 (72.0-85.6)	N/A
Adjuvant Therapy - **Adjuvant Therapy** - **No Adjuvant**	244 22	0.60 (0.18-1.96)	0.394	85.1 (79.0-89.4) 80.4 (49.7-93.4)	0.781	79.5 (71.7-85.4) 80.4 (49.7-93.4)	0.4802

		1.00					
Pre-referral surgery - **Prior surgery** - **No prior surgery**	96 170	1.18 (0.61-2.30) 1.00	0.630	82.6 (72.2-89.4) 85.5 (77.5-90.8)	0.0622	79.8 (67.8-87.7) 78.4 (67.5-86.0)	0.3758
Location - **Upper extremity** - **Lower extremity** - **Trunk**	64 179 23	1.13 (0.39-3.25) 1.00 0.89 (0.40-2.00)	0.821 0.769	85.8 (72.0-93.1) 85.1 (77.7-90.2) 77.7 (50.0-91.3)	0.8914	81.1 (63.5-90.8) 78.8 (69.0-85.8) 77.7 (50.0-91.3)	0.8442
Depth - **Deep** - **Superficial**	215 51	1.00 0.928 (0.44-1.98)	0.847	84.1 (77.0-89.2) 84.7 (70.6-92.4)	0.1717	79.1 (69.5-85.9) 78.7 (62.6-88.4)	0.5777
Size - **0-4cm** - **5-9cm** - **≥10cm**	66 100 100	1.00 1.66 (0.68-4.05) 1.71 (0.69-4.26)	 0.261 0.245	90.2 (79.5-95.5) 81.8 (70.3-89.1) 83.5 (72.7-90.4)	0.9367	86.6 (72.6-93.7) 73.5 (58.9-83.6) 80.7 (68.2-88.6)	0.4805
Margin - **Adequate** - **Inadequate**	248 18	1.00 2.75 (1.15-6.61)	 0.024*	87.0 (81.1-91.1) 63.1 (35.2-81.6)	0.001*	81.0 (72.9-86.9) 63.1 (35.2-81.6)	0.0016*

LRFS- Local recurrence-free survival
*Statistically significant

Table 4: Univariate analysis of prognostic factors for metastatic disease in 266 Undifferentiated Pleomorphic Sarcoma patients

Variable	No. of patients	MD LR (95%CI)	p value	5-year MFS % (95%CI)	p value	10-year MFS % (95%CI)	p value
Age - **70 years and older** - **Under 70 years**	101 165	1.09 (0.80-1.49) 1.00	0.594	56.9 (45.4-66.8) 64.8 (56.6-71.9)	0.7857	56.9 (45.4-66.8) 63.5 (55.1-70.8)	0.7332
Gender - **Male** - **Female**	144 122	1.35 (0.90-2.04) 1.00	0.148	57.1 (47.9-65.2) 67.9 (58.3-75.8)	0.0408*	57.1 (47.9-65.2) 65.8 (55.5-74.3)	0.1225

Local Recurrence at diagnosis - **Recurrence** - **No recurrence**	51 215	1.00 0.88 (0.52-1.48)	0.619	66.3 (50.8-77.9) 61.3 (53.8-67.9)	0.1422	62.8 (46.6-75.3) 61.3 (53.8-67.9)	0.6111
Metastases at diagnosis - **Metastases** - **No metastases**	17 249	3.51 (1.76-7.02) 1.00	<0.001*	Insufficient numbers Insufficient numbers	N/A	Insufficient numbers Insufficient numbers	N/A
Adjuvant Therapy - **Adjuvant Therapy** - **No Adjuvant**	244 22	0.34 (0.20-0.60) 1.00	<0.001*	64.4 (57.6-70.4) 38.1 (18.3-57.8)	0.0573	64.4 (57.6-70.4) 19.1 (1.7-50.9)	0.0016*
Pre-referral surgery - **Prior surgery** - **No prior surgery**	96 170	0.75 (0.49-1.16) 1.00	0.198	67.0 (55.9-75.9) 59.2 (50.9-66.7)	0.658	64.4 (52.5-74.1) 59.2 (50.9-66.7)	0.1391
Location - **Upper extremity** - **Lower extremity** - **Trunk**	64 179 23	0.99 (0.49-1.99) 1.00 0.98 (0.61-1.58)	0.978 0.940	61.5 (47.6-72.7) 62.6 (54.6-69.6) 59.5 (34.3-77.8)	0.6513	61.5 (47.6-72.7) 61.3 (53.0-68.6) 59.5 (34.3-77.8)	0.8388
Depth - **Deep** - **Superficial**	215 51	1.93 (1.07-3.49) 1.00	0.030*	58.5 (51.0-65.3) 75.6 (60.9-85.3)	0.9715	57.1 (49.2-64.2) 75.6 (60.9-85.3)	0.2561
Size - **0-4cm** - **5-9cm** - **≥10cm**	66 100 100	1.00 4.34 (1.93-9.79) 7.50 (3.37-16.7)	 <0.001* <0.001*	88.8 (77.8-94.5) 59.5 (48.4-69.1) 45.9 (35.1-56.0)	<<0.0011*	88.8 (77.8-94.5) 59.5 (48.4-69.1) 43.4 (32.3-54.1)	<<0.0011*
Margin - **Adequate** - **Inadequate**	248 18	1.19 (0.55-2.57) 1.00	0.658	61.7 (54.9-67.8) 64.3 (36.7-82.3)	0.5205	61.7 (54.9-67.8) 53.6 (24.4-75.9)	0.5766

MFS- Metastatic-free survival
*Statistically significant

Variable	No. of patients	Time to death HR	p value	Time to local recurrence HR	p value	Time to metastases HR	p value

Table 5: Multivariate analysis of 266 Undifferentiated Pleomorphic Sarcoma patients

Age - **Each additional year older**	266	1.03 (1.02-1.05)	<0.001*	1.03 (1.00-1.05)	0.046*	1.01 (0.99-1.03)	0.201
Metastases at diagnosis - **Metastases** - **No metastases**	 17 249	2.89 (1.58-5.26)	0.001*	-	-	3.99 (1.97-8.06)	<0.001*
Adjuvant Therapy - **Adjuvant Therapy** - **No Adjuvant**	 244 22	0.99 (0.48-2.04)	0.983	-	-	0.34 (0.19-0.61)	<0.001*
Location - **Upper extremity** - **Lower extremity** - **Trunk**	 64 179 23	 0.57 (0.34-0.98) 1.00 0.53 (0.25-1.13)	 0.043* 0.105	-	-	-	-
Depth - **Deep** - **Superficial**	 215 51	0.89 (0.53-1.53)	0.685	-	-	1.03 (0.54-1.96)	0.921
Size - **0-4cm** - **5-9cm** - **≥10cm**	-	 1.00 0.93 (0.49-1.77) 1.20 (0.63-2.27)	 0.833 0.573	-	-	 1.00 4.42 (1.93-10.09) 6.80 (3.00-15.44)	 <0.001* <0.001*
Margin - **Adequate** - **Inadequate**	 248 18	-	-	2.68 (1.11-6.43)	0.028*	-	-

*Statistically significant