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Predicting the Prognosis of Undifferentiated Pleomorphic Soft Tissue Sarcoma: A 20-year Experience of 266 Cases

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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 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 (5-9 cm [$p<0.001$; 4.42], ≥ 10 cm [$p<0.001$; 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.

Keywords: Undifferentiated pleomorphic sarcoma; Malignant fibrous histiocytoma; Prognosis; Soft tissue sarcoma

Abbreviations: MFH: Malignant Fibrous Histiocytoma; UPS: Undifferentiated Pleomorphic Sarcoma; STS: Soft Tissue Sarcoma; OS: Overall Survival; LR: Local Recurrence; MD: Metastatic Disease; CI: Confidence Interval; HR: Hazard Ratio.

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 high-grade sarcomas 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 present study is the largest of its kind.

Methods and Patients

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

Patients

The median patient age was 63.8 years (range19-94 years), with 144 males and 122 females. The lower extremity was the most commonly affected site. 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.

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Tumour

Upon commencing our study, 173 cases were initially categorised as MFH. All MFH tumours were re-categorised as per the new naming structure, by a specialist sarcoma pathologist. The remaining 101 were originally classified as UPS. A majority of the tumours (81%) were located deep in the soft tissue (subfascial) and were larger than 5 cm (75%). The average tumour size at presentation was 8.8 cm (range 1 cm to 55 cm), with the majority of tumours being located in the lower extremity (67%).

Treatment

There was no prior treatment for 170 cases presenting to St. Vincent's Hospital Melbourne, with the remaining 96 cases already having undergone excision at another institution. Inadequate margins were seen in 90% of patients who underwent excision at another institution prior to referral. All 266 patients referred to our centre underwent surgical excision, including those presenting with prior excision, regardless whether margins were adequate or inadequate.

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.

Two-hundred and forty-two patients (91%) underwent limb-sparing surgery; however, 24 patients (9%) required major amputation of the effected limb to ensure adequate margins. Of the 242 patients undergoing limb-sparing surgery, 226 (85%) had wide margin resections, 13(5%) had marginal margins and 5(2%) had intralesional resections. Postoperative radiotherapy was performed on 39% of patients with an inadequate margin (7/18). Adjuvant radiotherapy was administered to 91% of patients, compared to 3% of patients receiving adjuvant chemotherapy, as determined by our centre's sarcoma multi-disciplinary team.

Follow-up

Median follow-up was 7.8 years. A total of 8 patients were lost to review, receiving less than 12 months of follow-up. Hence 266 patients were included in the study. Post-treatment metastatic disease occurred in 100 patients (37.6%), as seen on the Kaplan-Meier analysis (Figure 1), 62% of all metastases arose within the first 24 months after surgery.

Prognostic factors and outcome measures

Tumour-related factors including gender, age, depth (in relation to the deep fascia), size, location, 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. Follow-up data was also collected including overall and disease-specific survival, local recurrence and metastatic disease, which were subsequently used as outcome measures.

Results

Disease outcome and patient survival

Median follow-up for patients was 85 months (range 12-217 months). At the time of final follow-up, the overall survival rate was 56% (149/266). Amongst those who had died, 72% had died of disease (85/118). A total of 7% of surviving patients were alive with disease at final follow-up (10/148). 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.

Local recurrence

Patient age (p= 0.034), local recurrence at diagnosis (p= 0.034) and surgical margin (p= 0.001) were all found to be significant prognostic factors, on univariate analysis, for developing local recurrence after definitive surgery at our institution (Table 1).

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	
- 0-4 cm	66 (24.8%)
- 5-9 cm	100 (37.6%)
- ≥ 10 cm	100 (37.6%)
- Average	8.8cm
- Standard Deviation	± 6.6 cm
- Range	1-55 cm
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%)
Grade	
- Low-grade	31 (18.2%)
- High-grade	139 (81.8%)
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 1: Clinicopathologic and treatment characteristics of 266 patients with undifferentiated pleomorphic sarcoma.

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%, respectively, for those <70 years. Local recurrence at the time of presentation, following pre-referral surgery, showed a higher rate of post-treatment local recurrence at 5-years, with 21.7% of those with a history of local recurrence and only 14.2% of those with no prior local recurrence. Patients who had inadequate surgical margins had a 2.75 times increased risk of developing local recurrence, when compared to patients with adequate margins.

Multivariate analysis revealed age (p= 0.046) and surgical margins (p=0.028) to be significant factors when predicting local recurrence after surgery, controlling for all other model covariates (Table 2). 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 local recurrence, when compared to adequate surgical margins.

Metastatic disease

Univariate analysis revealed that gender (p= 0.041), presence of metastases at diagnosis (P<0.001), adjuvant therapy (P<0.001), tumour depth (p= 0.030) and size (P<0.001) were significant prognostic factors for patients developing metastatic disease after definitive surgery at our institution (Table 3).

Development of metastatic disease was the only outcome measure for which gender had a significant impact on prognosis. Males had a higher rate of metastatic disease to females, at 5 years, with males having a metastatic rate of 43.1%, compared to 35.2% for females. 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. Just as with its effect on overall survival, the addition of adjuvant therapy saw a decrease in the rate of metastatic disease, with a 66% reduction in metastatic disease seen with the administration of adjuvant therapy. Tumour size was the most powerful adverse prognostic factor in determining the risk of developing metastatic disease, on univariate analysis. Tumours which were 5-9 cm had a 4.34 fold greater risk of death than those < 5 cm, and those ≥ 10 cm had a 7.50 fold greater risk of mortality than those <5 cm. The difference in 5-year metastatic rates between the groups <5 cm, 5-9 cm and ≥ 10 cm, were 11.2%, 40.5% and 54.1%, respectively.

Metastatic disease at diagnosis (P<0.001), adjuvant therapy (P<0.001) and size (P<0.001) were significant on multivariate analysis for predicting post treatment metastases (Table 2). Tumours sized 5-9 cm had a 4.42 fold increased risk of developing metastatic disease, when compared to smaller tumours. There was a further increase in risk of metastatic disease when tumours grew to ≥ 10 cm, with the risk increasing to 6.80 times that of tumours <5 cm.

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	0.575	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)		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 (0.29-1.22)	0.155	59.9 (35.2-77.7)		59.9 (35.2-77.7)	
Depth							
- Deep	215	1.73 (1.05-2.84)	0.030*	57.1 (49.6-63.9)	0.7098	45.4 (36.9-53.6)	0.2072
- Superficial	51	1.00		70.8 (55.6-81.6)		63.6 (48.0-75.7)	
Size							
- 0-4 cm	66	1.00		78.3 (64.6-87.1)	<0.0013*	72.5 (57.2-83.0)	<0.0011*
- 5-9 cm	100	2.08 (1.17-3.68)	0.012*	60.7 (49.5-70.1)		50.0 (37.3-60.6)	
- ≥ 10 cm	100	3.37 (1.93-5.87)	<0.001*	47.2 (36.5-57.1)		35.3 (24.6-46.3)	
Grade							
- High grade	139	1.38 (0.78-2.44)	0.269	57.5 (48.8-65.2)	0.0691	45.9 (37.0-54.4)	0.3317
- Low grade	31	1.00		67.7 (48.4-81.2)		60.6 (41.1-75.4)	
Margin							
- Adequate	248	1.00	0.123	60.9 (54.0-67.1)	0.3622	51.8 (44.1-58.9)	0.0748
- Inadequate	18	1.57 (0.88-2.80)		45.6 (22.5-66.1)		27.4 (9.4-49.1)	

OS- Overall Survival
*Statistically significant

Table 2: Univariate analysis of prognostic factors for overall survival 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	101	1.63 (0.93-2.88)	0.090	77.4 (65.7-85.5)	0.034*	71.9 (58.1-81.8)	0.0413*
- Under 70 years	165	1.00		88.4 (81.2-92.9)		83.3 (73.7-89.7)	
Gender							
- Male	144	0.81 (0.42-1.55)	0.531	84.8 (76.0-90.5)	0.6611	81.5 (71.6-88.2)	0.7631
- Female	122	1.00		84.2 (75.1-90.1)		76.5 (63.5-85.3)	
Local Recurrence at diagnosis							
- Recurrence	51	1.51 (0.73-3.12)	0.269	78.3 (62.1-88.2)	0.0336*	74.4 (56.8-85.6)	0.2128
- No recurrence	215	1.00		85.8 (79.1-90.5)		80.1 (71.1-86.6)	
Metastases at diagnosis							
- Metastases	17	2.99 (0.90-9.91)	0.074	Insufficient numbers	N/A	Insufficient numbers	N/A
- No metastases	249	1.00		85.2 (79.2-89.5)		79.8 (72.0-85.6)	
Adjuvant Therapy							
- Adjuvant Therapy	244	0.60 (0.18-1.96)	0.394	85.1 (79.0-89.4)	0.781	79.5 (71.7-85.4)	0.4802
- No Adjuvant	22	1.00		80.4 (49.7-93.4)		80.4 (49.7-93.4)	
Pre-referral surgery							
- Prior surgery	96	1.18 (0.61-2.30)	0.630	82.6 (72.2-89.4)	0.0622	79.8 (67.8-87.7)	0.3758
- No prior surgery	170	1.00		85.5 (77.5-90.8)		78.4 (67.5-86.0)	
Location							
- Upper extremity	64	1.13 (0.39-3.25)	0.821	85.8 (72.0-93.1)	0.8914	81.1 (63.5-90.8)	0.8442
- Lower extremity	179	1.00		85.1 (77.7-90.2)		78.8 (69.0-85.8)	
- Trunk	23	0.89 (0.40-2.00)	0.769	77.7 (50.0-91.3)		77.7 (50.0-91.3)	
Depth							
- Deep	215	1.00		84.1 (77.0-89.2)	0.1717	79.1 (69.5-85.9)	0.5777
- Superficial	51	0.928 (0.44-1.98)	0.847	84.7 (70.6-92.4)		78.7 (62.6-88.4)	
Size							
- 0-4 cm	66	1.00		90.2 (79.5-95.5)	0.9367	86.6 (72.6-93.7)	0.4805
- 5-9 cm	100	1.66 (0.68-4.05)	0.261	81.8 (70.3-89.1)		73.5 (58.9-83.6)	
- ≥ 10 cm	100	1.71 (0.69-4.26)	0.245	83.5 (72.7-90.4)		80.7 (68.2-88.6)	
Grade							
- High grade	139	0.651 (0.90-1.46)	0.299	84.3 (76.1-89.9)	0.9423	78.5 (68.5-85.6)	0.4408
- Low grade	31	1.00		75.5 (55.3-87.6)		70.1 (48.3-84.1)	
Margin							
- Adequate	248	1.00		87.0 (81.1-91.1)	0.001*	81.0 (72.9-86.9)	0.0016*
- Inadequate	18	2.75 (1.15-6.61)	0.024*	63.1 (35.2-81.6)		63.1 (35.2-81.6)	

LRFS- Local recurrence-free survival
*Statistically significant

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

Overall survival

Univariate analysis revealed that older age (P<0.001), presence of metastases at diagnosis (P<0.001), adjuvant therapy (P<0.001), tumour depth (p= 0.030) and size (P<0.001) were significant prognostic factors for patient overall survival (Table 4).

Patients aged ≥ 70 years had a 1.81 times greater risk of death than those <70 years. The 5-year and 10-year OS were 46.4% and 31.5%, respectively, for those ≥ 70 years rates were 68.0% and 60.3%, respectively, for those <70 years. Local recurrence 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 located deep to the muscular fascia had a 73% increase in mortality, as did large tumours, with those 5-9 cm having a 108% greater risk of death than those <5 cm, and those ≥ 10 cm having a 268% greater risk of mortality than those <5 cm. Metastatic disease at the time of presentation also had a significant impact on survival, with a 5.56 fold reduction in patient survival, as compared to those who presented metastasis-free (Table 5).

Comparison within groups on univariate analysis found inadequate margins were associated with 1.82 times the rate of death relative to wide margins (95% CI 1.01-3.27; p=0.045). Furthermore, radical margins were associated with 3.59 times the rate of death relative to wide margin (95% CI 2.07-5.54; p<0.001). This was supported by multivariate analysis revealing radical margins were associated with 2.89 times the rate of death relative to wide margins (95% CI 1.43-5.83; p=0.002).

Subsequent multivariate analysis showed age (P<0.001), metastases at diagnosis (p= 0.001) and tumour location (p= 0.043) to be statistically significant prognostic indicators, controlling for all other model covariates (Table 2). Every 1 year older at diagnosis was associated with 1.03 times the rate of death. Metastatic disease at diagnosis was associated with 2.89 times the rate of death. There was a 43% reduction in the rate of death in upper extremity tumours (HR=0.57) relative to a lower extremity location. Radical margins were associated with 2.89 times the rate of death, relative to wide margin.

Discussion

The former classification of MFH consisted of a wide range of histological appearances [4]. The term 'MFH' is now a confirmed 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, not otherwise specified sarcomas, now as UPS, account for only 5% of adult STS [21].

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	101	1.09 (0.80-1.49)	0.594	56.9 (45.4-66.8)	0.7857	56.9 (45.4-66.8)	0.7332
- Under 70 years	165	1.00		64.8 (56.6-71.9)		63.5 (55.1-70.8)	
Gender							
- Male	144	1.35 (0.90-2.04)	0.148	57.1 (47.9-65.2)	0.0408*	57.1 (47.9-65.2)	0.1225
- Female	122	1.00		67.9 (58.3-75.8)		65.8 (55.5-74.3)	
Local Recurrence at diagnosis							
- Recurrence	51	1.00	0.619	66.3 (50.8-77.9)	0.1422	62.8 (46.6-75.3)	0.6111
- No recurrence	215	0.88 (0.52-1.48)		61.3 (53.8-67.9)		61.3 (53.8-67.9)	
Metastases at diagnosis							
- Metastases	17	3.51 (1.76-7.02)	<0.001*	Insufficient numbers	N/A	Insufficient numbers	N/A
- No metastases	249	1.00		Insufficient numbers		Insufficient numbers	
Adjuvant Therapy							
- Adjuvant Therapy	244	0.34 (0.20-0.60)	<0.001*	64.4 (57.6-70.4)	0.0573	64.4 (57.6-70.4)	0.0016*
- No Adjuvant	22	1.00		38.1 (18.3-57.8)		19.1 (1.7-50.9)	
Pre-referral surgery							
- Prior surgery	96	0.75 (0.49-1.16)	0.198	67.0 (55.9-75.9)	0.658	64.4 (52.5-74.1)	0.1391
- No prior surgery	170	1.00		59.2 (50.9-66.7)		59.2 (50.9-66.7)	
Location							
- Upper extremity	64	0.99 (0.49-1.99)	0.978	61.5 (47.6-72.7)	0.6513	61.5 (47.6-72.7)	0.8388
- Lower extremity	179	1.00		62.6 (54.6-69.6)		61.3 (53.0-68.6)	
- Trunk	23	0.98 (0.61-1.58)	0.940	59.5 (34.3-77.8)		59.5 (34.3-77.8)	
Depth							
- Deep	215	1.93 (1.07-3.49)	0.030*	58.5 (51.0-65.3)	0.9715	57.1 (49.2-64.2)	0.2561
- Superficial	51	1.00		75.6 (60.9-85.3)		75.6 (60.9-85.3)	
Size							
- 0-4 cm	66	1.00		88.8 (77.8-94.5)	<<0.0011*	88.8 (77.8-94.5)	<<0.0011*
- 5-9 cm	100	4.34 (1.93-9.79)	<0.001*	59.5 (48.4-69.1)		59.5 (48.4-69.1)	
- ≥ 10 cm	100	7.50 (3.37-16.7)	<0.001*	45.9 (35.1-56.0)		43.4 (32.3-54.1)	
Grade							
- High grade	139	1.81 (0.86-3.79)	0.118	58.8 (49.8-66.7)	0.0656	57.7 (48.6-65.7)	0.1254
- Low grade	31	1.00		72.3 (52.3-85.2)		72.3 (52.3-85.2)	
Margin							
- Adequate	248	1.19 (0.55-2.57)	0.658	61.7 (54.9-67.8)	0.5205	61.7 (54.9-67.8)	0.5766
- Inadequate	18	1.00		64.3 (36.7-82.3)		53.6 (24.4-75.9)	

MFS- Metastatic-free survival
*Statistically significant

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

Variable	No. of patients	Time to death HR	p value	Time to local recurrence HR	p value	Time to metastases HR	p value
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	17	2.89 (1.58-5.26)	0.001*	-	-	3.99 (1.97-8.06)	<0.001*
- No metastases	249						
Adjuvant Therapy							
- Adjuvant Therapy	244	0.99 (0.48-2.04)	0.983	-	-	0.34 (0.19-0.61)	<0.001*
- No Adjuvant	22						
Location							
- Upper extremity	64	0.57 (0.34-0.98)	0.043*	-	-	-	-
- Lower extremity	179	1.00					
- Trunk	23	0.53 (0.25-1.13)	0.105				
Depth							
- Deep	215	0.89 (0.53-1.53)	0.685	-	-	1.03 (0.54-1.96)	0.921
- Superficial	51						
Size							
- 0-4 cm	-	1.00		-	-	1.00	
- 5-9 cm		0.93 (0.49-1.77)	0.833			4.42 (1.93-10.09)	<0.001*
- ≥ 10 cm		1.20 (0.63-2.27)	0.573			6.80 (3.00-15.44)	<0.001*
Margin							
- Adequate	248	-	-	2.68 (1.11-6.43)	0.028*	-	-
- Inadequate	18						

*Statistically significant

Table 5: Multivariate analysis of 266 undifferentiated pleomorphic sarcoma patients.

The key purpose of our study was to identify independent prognostic factors in a well-documented cohort of 266 cases of UPS. Lehnhardt et al. study [19] of 140 patients is the only study analysing UPS tumours and stratifying for prognostic factors, measuring for overall survival and local recurrence. There are numerous adverse prognostic factors identified by other studies which align with our analysis. These include large tumour size [10,12,14,16-19,25-27], metastases at presentation [12], tumour depth [14,16,26,28], presentation with local recurrence [16,18,19], older age [14,16,27] and positive surgical margins [10,12,14,18,19,27].

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 local recurrence. Local recurrence rates as high as 30% were reported prior to the use of radiotherapy [29-32]. A dramatic drop in the local recurrence rate to below 15% was seen when combined radiotherapy and surgery was introduced [7].

Multivariate analysis revealed the use of adjuvant radiotherapy was associated with a 66% reduction in metastatic disease. Our findings are supported by randomised control trials which have confirmed that surgery combined with radiotherapy is the most effective management for most localised high-grade STS [29-31].

Wide surgical resection margin is the most important post-operative prognostic factor in STS subtypes [19]. Lehnhardt's UPS study revealed negative margin tumours having a 79% 5-year OS, positive margins 23% and intralesional having 0% of patients surviving at 5 years [19]. Our study revealed a trend toward poorer overall survival for inadequate margins, with univariate and multivariate analysis showing inadequate margins leading to a significantly higher risk of developing local recurrence (Tables 2-3).

Intralesional excisions in our cohort were performed with the intent of palliative management, as de-bulking surgery provided symptom relief. Those who underwent an intralesional excision had a 0% overall survival (OS) at 5-years, with the mean OS being 1.39 years after surgery.

Older age at diagnosis has been shown to be an adverse prognostic indicator in our univariate (overall survival, metastatic disease) and multivariate (metastatic disease) analyses. Past studies have shown that young age at diagnosis is correlated with better survival and reduced local recurrence compared to those of older age [14,16,27]. Reasoning behind reduced overall survival of older patients, is attributable to elderly patients having a greater number of medical co-morbidities. Increased incidence of local recurrence in the elderly, reported in the literature, has been attributed to less aggressive therapy, with lower rates of radiotherapy, chemotherapy and wide resections in older patients [33].

Tumours are widely described as being located deep or superficial in the soft tissue, based on its correlation to the investing muscular fascia. Our findings revealed deep-seated tumours had a 73% increase in mortality and 93% increase in metastatic disease, when compared to superficial tumours. This can be explained by the fact that deeper tumours are less palpable and visible in the early stages of disease, allowing them to grow larger, cycling through a greater number of cell divisions, in-turn increasing the aggressiveness of the tumour. Greater vascularisation of deep tumours also contributes to their ability to more readily spread.

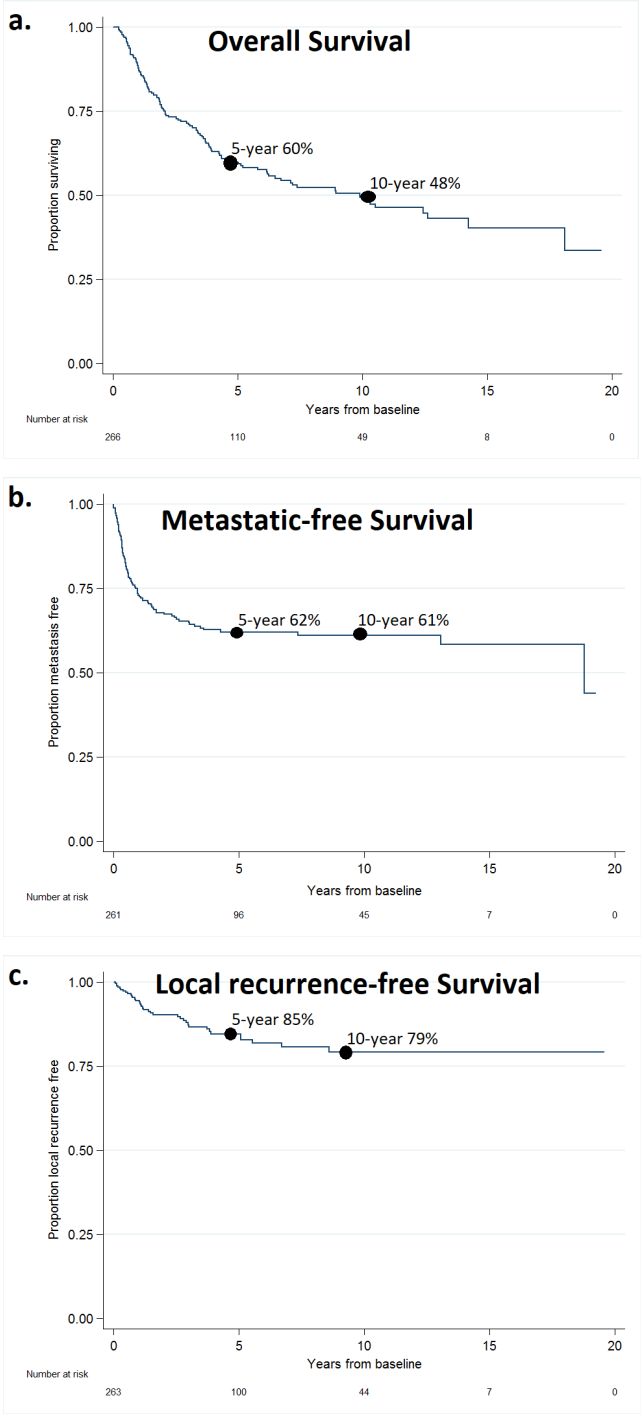

Figure 1: Kaplan-Meier curves.

Superficial tumours are routinely smaller than deep tumours, as they are noticed earlier. Our cohort's mean superficial tumour size was 5.6 cm, versus 9.6 cm for deep tumours, with only 8% of tumours ≥ 10 cm being located superficially. Similarly, Salo et al. cohort of MFH tumours showed 11% of all large tumours (>10 cm) were located superficially. Additionally, they found superficial tumours were significantly associated with improved disease-specific survival [16].

Local recurrence at the time of referral was seen in 51 of the 96 patients who presented to our centre after excision elsewhere. This group had a 68% increased risk of mortality and an 8% higher 5-year post-treatment rate of local recurrence, underpinning the importance of sarcoma specialist centre management over non-sarcoma centre care.

In our study, 75 of 100 metastases occurred in the absence of local recurrence. Additionally, of the 21 cases where patients had both local recurrence and metastatic disease after definitive surgery, 11 (52%) had distant metastases occur prior to local recurrence. This indicates local recurrence may occur in the presence or the absence of metastases, meaning the presence alone of the local recurrence is not an accurate predictor of metastases. There is some conjecture with these findings, as studies have shown that the timing of local recurrence to be predictive of metastatic disease [19,34]. If local recurrence occurs in the presence of metastatic disease, it likely reflects the local manifestations of a systemically aggressive tumour.

Tumours located in the lower extremity have a higher association with poorer survival, with our cohort revealing a 43% increase in risk of mortality, when compared to upper extremity and truncal tumours. A possible cause for this is that the lower extremities have a larger soft tissue mass, allowing the tumour to increase in size before detection.

Large tumour size is the most widely reported negative prognostic factor for UPS and MFH tumours [10,12,14,16-19,26]. Our findings support this trend, with increasing size being associated with increased mortality and metastatic disease. The 5-year overall survival rates for tumours sized 0-4 cm, 5-9 cm and ≥ 10 cm were 78.3%, 60.7% and 47.2%, respectively. Comparably significant results are seen in our cohort's 10-year overall survival as well as 5 and 10-year metastatic disease rates. The most powerful multivariate finding in our study was the 580% increase in the risk of metastatic disease for tumours ≥ 10 cm, when compared to smaller (0-4 cm) lesions. Zagar et al. analysis of 271 MFH tumours similarly revealed a significant increase in metastatic disease risk, with a near-double risk when comparing tumours <10 cm and ≥ 10 cm.

Further underpinning the significance of size on outcome, we identified that those with tumours >15 cm in our cohort had a 10-year overall survival of only 4% (1/27). A primary theory 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.

Conclusion

UPS is a rare, high-grade, STS manifesting itself in a variety of histologic appearances, the most common being a mixture of storiform and pleomorphic areas. UPS 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. This is only the second multivariate analysis performed pertaining to UPS prognostic factors, and is the largest of its kind.

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.

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