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Extra-Thoracic Solitary Fibrous Tumours: Outcomes and Prognosis

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Abstract

Introduction: Solitary fibrous tumours (SFTs) are rare spindle cell neoplasms and have been described according to location as intra-thoracic and extra-thoracic. The World Health Organization classifies SFT as having intermediate malignant potential with low risk of metastasis. Initially extra-thoracic SFTs (ESFT) were considered to be benign with lower rates of mortality when compared to their thoracic counterpart. However, more recent series have found that ESFT behave more aggressively than previously thought. Our tertiary referral centre for soft tissue sarcoma has seen a significant proportion of aggressive disease associated with ESFT.

Methods: A review of all patients with a pathological diagnosis of ESFT was carried out between 2006 and 2019. Histopathology data was reviewed and a database was created to record patient demographics as well as follow up data including recurrence, metastases and survival. Statistical analyses were carried out.

Results: A total of 95 patients were reviewed of which 75 had both biopsy and resection data. 29% of tumours were classified as malignant (MSFT) and 71% tumours were classified as benign (ESFT) after resection. We noted that 50% for patients with MSFT were initially benign ESFT on initial biopsy.

Conclusion: Our study showed that 50% of biopsies for patients with MSFT were initially benign and we feel this has important surgical considerations. Certain prognostic factors are important to help risk stratify these patients. We would recommend that patients with ESFT should be kept under surveillance in a manner similar to patients with malignant soft tissue sarcomas.

Keywords: Solitary Fibrous Tumour; Soft Tissue Sarcoma; Surgical Oncology; Sarcoma; Orthopaedic Oncology

Abbreviations: Solitary Fibrous Tumour (SFT); Extra-Thoracic Solitary Fibrous Tumour (ESFT); Malignant Extra-Thoracic Solitary Fibrous Tumour (MSFT); World Health Organisation (WHO)

Introduction

Solitary fibrous tumours (SFT) are rare spindle cell neoplasms that account for less than 2% of all soft-tissue tumours [1]. The World Health Organization classifies these tumours as neoplasms of pluripotent fibroblastic or myofibroblastic origin [2]. Pathological classification includes a well-defined, lobulated firm mass which is fibrous, with a whorled appearance with intermixed areas of cystic degeneration, calcification, haemorrhage and necrosis macroscopically [3]. Microscopically, they consist of 'whorls of reticulin and collagen with interspersed spindle-shaped cells [2]. SFT were initially described as intra-thoracic however these tumours have been subsequently discovered in extra-thoracic locations such as head, neck, breast, abdomen, pelvis and extremities [1]. Radiological identification is particularly difficult of the extra-thoracic SFT [1]. Immunohistochemical analysis plays an important role in the diagnosis of these tumours as 60-70% of benign SFT is positive for CD34 antibody and may be positive for bcl-2 and vimentin [4, 5]. There is increased expression of cytokeratin, S-100, and p53 proteins in malignant solitary fibrous tumours [5].

WHO classifies these tumours as having intermediate malignant potential with low risk of metastasis [2, 6]. Initial series reported SFT to originate exclusively from the pleural and thoracic cavity (thoracic SFT) of which 10 to 36% had malignant pathology [7-10]. Since extra-thoracic SFTs (ESFT) have been considered separately, an initial series reported ESFT to be benign with lower rates of recurrence of 6% and mortality of 1% when compared to their thoracic counterpart [11]. More recent series have contradicted this and found that ESFT behave more aggressively than previously thought, with increased rates of local recurrence, increased rate of distant metastasis and decreased survival months, similar to thoracic SFT [12, 13].

The treatment of choice for ESFT is surgical resection with or without adjuvant chemotherapy or radiotherapy [1]. A recent systematic review of 100 articles of ESFT between 1970 to 2016 reported overall median 5 and 10-year survival rates as 59-100% and 40-89% respectively [14]. They noted certain prognostic indicators such as presence of malignant features on pathology, tumour location and size and incomplete resection margins to be associated with increased locoregional recurrence and reduced survival. They also discussed that both benign and malignant ESFT are associated with recurrence and metastasis. There are currently very few studies looking at clinical outcome from ESFT and there is no official guideline to for follow up surveillance [14].

Our tertiary referral centre for soft tissue sarcoma has seen a significant proportion of aggressive disease associated with ESFT along with follow up data. This study aims to review cases of ESFT and relate tumour characteristics and histopathological findings with prognosis and clinical outcomes.

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Materials and Methods

Study Design and Participants

A review of all patients with a pathological diagnosis of ESFT was carried out between 2006 and 2019. Ninety-five patients were identified during this 13-year time period; the relevant biopsy and resection histopathology data was reviewed using the hospital electronic patient record system. A database was created to record patient demographics, diagnosis, tumour size, tumour site, tumour depth and surgical resection margins. Clinic notes were reviewed to record follow up data including adjuvant therapy, local recurrence, metastases and survival months for cases with at least two-year follow up data.

Statistical Analysis

The aim of all analyses was to examine the association between patient and tumour characteristics in relation to three outcomes: recurrence, metastasis and survival. As there were several factors of interest, the analyses were performed using regression methods. The specific method was dependent on the nature of outcome variable.

For each outcome, the analyses were performed in two stages. Initially, a series of univariable analyses examined the association between each factor and the outcome. The second stage of the analysis examined the joint association between the factors and the outcome in a single multivariable analysis. To restrict the number of variables in this second stage in the analysis, only variables showing some association with the outcome in the univariable analyses ($p<0.2$) were considered. To retain only the statistically significant variables in the final model, a backwards selection procedure was used. This involves omitting non-significant variables, one at a time, until only significant variables remained.

Both recurrence and metastasis were binary (yes/no) outcomes. Due to this characteristic, the analysis for these outcomes was performed using logistic regression. The exception to the above method of analysis was when there were no recurrences in one category of a variable. In such a situation, logistic regression cannot be used, and the analysis was instead performed using Fisher's exact test. Survival analysis methods were used to analyse patients over survival; by using a time to death or time last known to be alive. Due to the survival nature of the outcome, the analysis was performed using Cox regression.

There was no source of funding for this study.

Results

A total of 95 patients had a diagnosis of ESFT on biopsy or resection histology between 2006 and 2019. Of these 75 were eligible for the study. 20 patients met the exclusion criteria. Five patients were excluded because of thoracic SFT location. 12 patients only had biopsy data and no resection data. Two patients had myxoid spindle cell lipoma as the diagnosis and one patient had atypical lipomatous tumour as the diagnosis. The remaining 75 patients who were used for analysis in the study had biopsy and resection data. 14 of these patients were diagnosed between 2017-2019 and therefore follow up data (recurrence, metastasis, survival) was not analysed for these cases.

Demographics

There were 36 women and 39 men with an age range of 18 to 85 years with a mean age of 54 years. 22 tumours were classified as malignant and 53 tumours were classified as benign. Patient, tumour characteristics as well as anatomical location are presented in (Table 1).

Table 1: Patient and tumour characteristics of 75 extra-thoracic solitary fibrous tumours.

Characteristic		Value
Median age (range)		53 yrs (18-85 yrs)
Gender	Male (%)	39 (52)
	Female (%)	36 (48)
Tumour size *	Average (mm)	6.7 x 4.5 x 3.7
	<50 mm (%)	27 (36)
	50-100 mm (%)	30 (40)
	>100 mm (%)	16 (21)
	Fragmented	2 (3)
Tumour depth	Superficial (%)	17 (23)
	Deep (%)	55 (73)
	Bone (%)	3 (4)
Pathological classification	Benign (%)	53 (71)
	Malignant (%)	22 (29)
Anatomical location	Lower limb (%)	45 (60)
	Upper limb (%)	19 (25)
	Head and neck (%)	1 (1)
	Pelvis (%)	5 (7)
	Trunk (%)	5 (7)

*Tumour size was taken as the largest size from the reported length, width and depth

Biopsy and resection pathological diagnosis

Of the 22 patients with malignant features on resection specimen, 20 patients had both biopsy and resection histological diagnoses. 10/20 had a biopsy diagnosis of benign ESFT and resection diagnosis showed malignant features (MSFT). 5/20 had a biopsy diagnosis other than ESFT (1 round cell sarcoma and 4 spindle cell sarcoma) and went to have a resection, which showed malignant SFT: 4/20 patients had both malignant features (MSFT) on biopsy and resection. 1/20 patient had a diagnosis of SFT on biopsy and adenocarcinoma on resection.

We note that 50% of biopsies for patients with MSFT were initially benign ESFT and we feel this has important surgical considerations.

Clinical outcomes

a) Recurrence

There was data on recurrence for 61 patients. Recurrence occurred in 7/61 patients (11%). (95% confidence interval: 5% to 22%). Univariable analyses were performed to examine factors associated with a recurrence.

The results suggest that both histological diagnosis and tumour location are statistically significant factors when it comes to predicting tumour recurrence. A recurrence occurred in 35% of MSFT patients, but only 2% of ESFT patients. The odds of a recurrence were over 20 times higher for MSFT patients than for ESFT patients. The statistical analysis for tumour location suggested similar levels of recurrence in the lower limb and upper limb areas (around 5%). Recurrence was much higher in the pelvis/trunk area, where the recurrence rate was 50% and 80% of tumours in the pelvis were malignant SFT. The odds of recurrence in the pelvis/trunk area were 17 times higher than in the lower limb area. The remaining variables were not found to be significantly associated with a recurrence.

b) Metastasis

Overall rate of metastasis in both benign and malignant ESFT was 8 out of the 61 (13%) patients with data. (95% confidence interval: 6% to 24%).

The results suggested that histological diagnosis, tumour location and mitotic count were statistically significant with regards to metastasis when examined individually. However, there was no significant association with margins, tumour size or tumour depth. Metastasis was more common in MSFT patients, where it occurred in over 40% patients, than benign ESFT patients (2%). The odds of metastasis were 30 times greater in MSFT patients than in benign ESFT patients. The pelvis/trunk location had the highest occurrence of metastasis with half of all patients with this tumour location having developing metastatic disease, compared to less than 10% of patients in the other outcomes. The odds of metastasis were 11 times higher in the pelvis/trunk location compared to the lower limb. Additionally, 80% of the tumours in the pelvis/trunk location were malignant ESFT. A higher mitotic count was also associated with a greater chance of metastasis. Those in the ≥ 4/10 had odds of metastasis that were over 12 times higher than those with a lower count.

c) Survival

Initially the survival of the group as a whole was examined. The data suggested that the median survival time for all patients was 8.0 years. When examining individual factors, only histological diagnosis was found to be significantly associated with patient survival (p 0.005). Survival was shorter in the MSFT who had a median survival time of 5 years, contrasting with a median survival of 11 years for the SFT group. The risk of death at any time in the MSFT group was 6.5 times greater than in the benign ESFT group. A graphical illustration of the survival times for the two diagnosis groups are shown in Figure 1. None of margins, tumour location, mitotic count, tumour size and tumour depth were significantly associated with survival times Table 2.

Adjuvant therapy

Complete resection was achieved in 73/75 cases, two cases had fragmented tumour specimen. Adjuvant therapy data and treatment regimens were reviewed for patients who presented between 2006–2016 (52 cases). 10/52 cases had malignant features on tumour resection data and were treated with neoadjuvant therapy. Specifically, 2 out of 10 cases were treated with both post-operative radiotherapy and chemotherapy, 7 out of 10 had post-operative radiotherapy only and 1 case had post-operative chemotherapy only. The chemotherapy regimes used included VDC/IE (vincristine doxorubicin and cyclophosphamide / ifosfamide and etoposide over 5 days for 3 cycles), doxorubicin and gemcitabine, and one patient had palliative chemotherapy. The radiotherapy regimes ranged from 50-66Gy in 30# and one patient had palliative radiotherapy 30Gy in 30#. 7 out of the 10 patients died from the disease with a mean survival of 43 months. 1 patient had 88 survival months but died from other disease (breast carcinoma). 2 patients are currently alive, one has 27 follow up months and one has 88 months follow up.

In conclusion, the results showed that histological diagnosis and tumour location were significantly associated with recurrence and metastasis. Mitotic count was significantly associated with metastasis only and histological diagnosis was significantly associated with survival months.

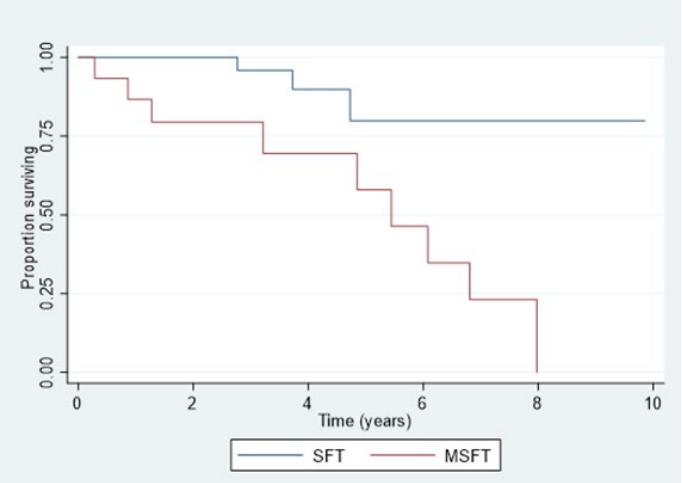

Figure 1: Kaplan-Meier plot of time to death by histological diagnosis.

Table 2: Univariable associations with recurrence, metastasis and survival times.

		Recurrence			Metastasis			Survival		
	Category	**n/N (%)**	**Odds Ratio (95% CI)**	**P-value**	**n/N (%)**	**Odds Ratio (95% CI)**	**P-value**	**Survival years, Median [IQR]**	**Hazard ratio (95% CI)**	**P-value**
Histological diagnosis	Benign ESFT	1/44 (2%)	1	0.005	1/44 (2%)	1	0.002	11.1 [11.1, 11.1]	1	**0.005**
	MSFT	6/17 (35%)	23.5 (2.55, 216)		7/17 (41%)	30.1 (3.32, 273)		5.4 [3.2, 6.8]	6.50 (1.75, 4.2)	
Margins	Negative	5/44 (11%)	1	0.57	5/44 (11%)	1	0.9	8.0 [5.4, 11.1]	1	0.34
	Marginal/Positive	1/16 (6%)	0.52 (0.06, 4.83)		2/13 (13%)	1.11 (0.19, 6.41)		# [3.7, #]	1.98 (0.48, 8.13)	
Tumour location (*)	Lower limb	2/37 (5%)	1	0.009	3/37 (8%)	1	0.02	8.0 [4.7, 11.1]	1	0.82
	Upper limb	1/16 (6%)	1.17 (0.10, 13.9)		1/16 (6%)	0.76 (0.07, 7.89)		# [#, #]	0.68 (0.14, 3.31)	
	Pelvis/trunk	4/8 (50%)	17.5 (2.40, 128)		4/8 (50%)	11.3 (1.84, 70.0)		6.8 [6.1, #]	17.5 (0.30, 4.96)	
Mitotic count	<4/10	2/37 (5%)	1	0.15	1/37 (3%)	1	0.02	# [5.4, #]	1	0.15
	≥ 4/10	4/23 (17%)	3.68 (0.62, 22.0)		6/23 (26%)	12.7 (1.42, 114)		6.8 [6.1, 8.0]	2.50 (0.72, 8.66)	
Tumour size	<50mm	++	++	0.12	1/21 (5%)	1	0.14	# [#, #]	1	0.4
	50-100mm	2/45 (4%)	1		2/24 (8%)	1.82 (0.15, 21.6)		# [6.8, #]	1.08 (0.18, 6.51)	
	>100mm	2/10 (20%)	5.38 (0.66, 43.9)		3/10 (30%)	8.57 (0.76, 96.5)		6.1 [3.2, 8.0]	2.58 (0.47, 14.1)	
Tumour depth (**)	Superficial	0/0 (0%)	(+)	0.58	0/0 (0%)	(+)	0.58	# [#, #]	1	0.89
	Deep	6/48 (13%)	(+)		6/48 (13%)	(+)		# [6.8, #]	1.15 (0.14, 9.36)	

(*) Omitting one patient with head/neck tumour location

(**) Omitting two patients with 'bone' response

(+) Unable to calculate odds ratio due to no recurrences / metastasis in one group. Analysis using Fisher's exact test

(#) Unable to calculate survival summary due to an insufficient number of deaths in this group

Discussion

SFT were initially described as intra-thoracic however these tumours have been subsequently discovered in extra-thoracic locations including head and neck, abdomen, pelvis, retroperitoneum, breast and extremities [14]. Initially, ESFT were reported to be benign with lower rates of recurrence of 6% and 1% mortality when compared to their thoracic counterpart [11] however, since extra-thoracic SFTs have been considered separately, there have been studies which show that ESFT may have increased rates of malignancy [12,13, 15]. There are very few studies that have analysed clinical outcomes of recurrence, metastasis and death in patients with extra-thoracic tumours.

Pathological classification

Our study showed 22 MSFT out of a total 75 cases (29%) from 2006 to 2019 which is correlates with the most recent literature review reporting a range of 11 to 33% malignant ESFT [13]. We were able to collect data on recurrence, metastasis and survival for cases with adequate follow up (n=61). Our overall rate of recurrence and metastasis for benign and malignant ESFT was 11% and 13% respectively with an overall median survival time of 8 years. There was a 40% metastasis and 35% recurrence rate for MSFT and 2% metastasis and recurrence rate for ESFT. We also found 30 times greater odds of metastasis and 20 times higher odds of recurrence in MSFT patients.

A large retrospective series of 92 ESFT reported 10 MSFT (11%) of which 8 developed local recurrence or metastasis (80%) [11]. However, follow up was only 24 months and they did not report any deaths. Another study reviewed 33 patients with ESFT and found 18 MSFT (55%) of which 13 developed recurrence or metastasis (72%) and a 40% 5- year survival rate for MSFT. In comparison, we had 29% MSFT and a similar, 75% rate of recurrence or metastasis and our data showed 6.5 greater risk of death for MSFT. We noticed that tumour recurrence or metastasis can occur up to 6 years after diagnosis (1 case resected in 2012 with recurrence in 2017, 1 case resected in 2008 with metastasis in 2014).

Malignant disease is suggested by one or more of the features :> 4 mitotic figures per 10 high power fields (HPF), presence of tumour necrosis, hypercellularity, atypia, nuclear pleomorphic and or vascular invasion [13]. In our review of pathological reports, mitotic count was the most consistent of these features to be commented on. Those reports with a benign ESFT diagnosis, 43/52 had mitotic count <4/10 HPF and those with malignant ESFT diagnosis, 21/26 80% had a mitotic count of >4/10 HPF. A higher mitotic count was significantly associated with a greater chance of metastasis. Those in the ≥ 4/10 had odds of metastasis that were over 12 times higher than those with a lower count. Furthermore, our study found that 50% of patients with malignant ESFT had an initial biopsy diagnosis of benign ESFT and were found to have malignant features only on resection data. We feel this has important surgical considerations such that all ESFT should be resected in a similar way to high grade soft tissue sarcoma, even if the initial biopsy diagnosis is benign.

Our study confirms that pathological classification remains an important prognostic indicator and perhaps mitotic count could be used to grade ESFT as <4/10 HPF and >4/10 HPF to aid assessment of prognosis and MDT management for treatment and follow up. Cranshaw et al. suggested that MSFT behave clinically similar to high-grade soft tissue sarcoma and we agree that these cases require be treated and followed up similarly with close surveillance [13].

Tumour location, size and depth

Gold et al found conducted a review of 75 patients and found that anatomical location was an independent prognostic indicator for ESFT disease recurrence [11]. Cranshaw et al found that abdominal, retroperitoneal or pelvic ESFT had an increased rate of disease recurrence and trend towards mortality despite adequate resection margins [13]. Given that our centre receives orthopaedic referrals, the majority of our referrals include SFT originating from upper and lower limbs and pelvis. Our study showed a significant association between tumour location and recurrence/metastasis. The tumour location results suggested similar levels of recurrence (around 5%) in the lower limb and upper limb areas. The most important finding was that pelvis/trunk tumour location had a significant association with negative clinical outcome. 80% of pelvis/trunk tumours had a malignant histological diagnosis as well as a much higher recurrence rate (50%) than other sites with 50% having metastasis. All other tumour sites had a rate of metastasis of less than 10%. This could be because tumours occurring in the pelvis are of larger size and it is widely accepted that larger tumours can have more malignant transformation [14]. However, a recent literature review reported that there is no uniform consensus on the exact diameter of tumour and significant effect on prognosis and that benign and malignant ESFT can be of varying size [14]. Our study also found that there was no significant association specifically with tumour size or tumour depth.

Adjuvant therapy

Neo-adjuvant therapy can be used to reduce the size of the tumour and aid surgical treatment [13]. Our patients received a range of 50-66Gy targeted radiotherapy which is similar to other studies [14] and can be used for pre or post-operative and palliative radiotherapy. All of our cases diagnosed as malignant were treated with neo-adjuvant therapy and 7/10 patients died from the disease despite radiotherapy and/or chemotherapy with a mean survival month of 43. Three patients who did not die from MSFT had post-operative radiotherapy and did not develop local recurrence. A study from Baldi et al conducted a review of 14 patients retrospectively who underwent post-operative radiotherapy and found that they developed metastasis in absence of local recurrence however these results also looked at thoracic SFT which is known to behave aggressively [16]. Although our study size is small, our results do show that local recurrence and metastasis can occur despite neoadjuvant therapy however the sample size was too small to draw significant statistical conclusions. Chemotherapy has been used particularly, doxorubicin and gematibicine as the most commonly used agents however these have shown poor outcomes so far in the literature, similar to our study. 3 patients who had chemotherapy developed metastases despite chemotherapy. Further to this study, it would be interesting to see the 'choi partial response' and progression free survival [14, 17, 18] however, again, our sample size is too small currently to conduct this analysis.

Treatment based on biopsies

We have also noted that 50% of the initial biopsies that were thought to be benign ESFT turned out to be MSFT. We feel this has important surgical consideration when it comes to excising these lesions. Given the fact that MSFT are associated with a higher rate of recurrence and metastasis all benign ESFT on biopsy should be surgically excised with a margin of healthy tissue, as opposed to marginal excisions alone.

Conclusion

ESFT is a rare spindle cell neoplasm which has higher rates of

recurrence, metastasise and malignancy than previously thought. Many studies have reviewed the histological data of ESFT however few have analysed the clinical outcomes and follow up data. Certain prognostic factors such as histological diagnosis, tumour location, presence of high mitotic count are important to help risk stratify and help identify those at risk of recurrence, metastasis and death. It is evident that there is a need for close surveillance as these tumours can behave aggressively and may have poor outcomes late on. In addition, we suggest that all ESFT should be resected in a similar way to high grade soft tissue sarcoma as 50% of cases with a benign diagnosis on initial biopsy, had malignant features on resection data. Surgical excision remains the mainstay of treatment however there may be a role for adjuvant therapy and further research is needed in this area.

We would recommend that patients with ESFT be kept under surveillance in a similar manor to those patients with malignant soft tissue sarcomas. Meaning these patients should be seen at regular intervals for clinical examinations and a chest x-ray for up to 10 years.

Declarations of Interest

None

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