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Epidemiology and survival factors of appendicular myxofibrosarcoma: a SEER-retrospective study

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ABSTRACT

Background: The low incidence of myxofibrosarcoma (MFS) makes high power studies difficult to perform. Demographic and prognostic factors for MFS and how they differ from all extremity soft tissue sarcomas (STS) are not well understood. The purpose of this study was to characterize a large cohort of patients with MFS and evaluate epidemiologic and survival factors when compared to all STS.

Materials and methods: We performed a retrospective review of the Surveillance, Epidemiology, and End Results (SEER) database from 2000 to 2015 to identify 1,440 patients diagnosed with MFS and 12,324 with STS. Survival curves were creased using Kaplan-Meier, and Cox regression analyses were performed to identify hazard ratios (HRs).

Results: Overall survival was greater for STS than MFS (79% *vs.* 67%). Patients with MFS had a higher average age at diagnosis than STS (62 *vs.* 56), and older age was strongly associated with decreased survivorship for MFS (HR = 7.94). A greater proportion of patients under 30 diagnosed with MFS were female when compared to STS (49.6% *vs.* 45.4%). The incidence of MFS and STS increased over the 15-year period, with MFS increasing at a greater rate than STS (1.25% *vs.* 2.59%). Survival increased for patients diagnosed after 2008 for both STS (9.4%) and MFS (13.2%).

Conclusions: There are differences between patient demographics and survival factors when comparing MFS to all STS. Monitoring changes in demographic and survival trends for rare STS subtypes like MFS is important to improve diagnostic algorithms and treatment options.

Key words: sarcoma; soft tissue sarcoma; malignancy; myxofibrosarcoma; surveillance; epidemiology

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Introduction

Myxofibrosarcoma (MFS) is a rare malignant soft tissue sarcoma (STS) subset of the heterogenous group of fibrohistiocytic tumors [1] with an estimated prevalence of < 0.1/100,000/years [2]. It is an aggressive soft tissue malignancy that presents with a high recurrence and metastatic rate. It commonly appears in elderly patients and in the extremities but can also occur in the trunk and head/neck region. Current clinical management for MFS is dependent on characteristics of the malignancy, including depth, size, grade, and episodes of previous recurrence [2]. MFS always requires surgical resection as part of the treatment plan and radiation therapy is generally supplementary to surgical treatment [3]. When compared to other STS, small cohort stud-

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ies have indicated a better disease specific survival rate than other sarcoma subtypes [4].

As a result of the low prevalence of this disease, only small heterogenous cohorts have been previously reported regarding patient and disease characteristics that impact prognosis. Identifying prognostic characteristics is vital for accurate clinical decision making, especially considering the variation of STSs in clinical behavior and treatment. Tumor grade, depth of invasion, and recurrence have all been associated with worse outcomes in the case of MFS in pilot clinical studies [4]. However, large scale conglomerate data is needed to confirm prognostic characteristics and survival rates in patients with this STS.

To date there have been no large-scale population-based studies comparing outcomes, survival factors, and prognostic factors of MFS to all STS. One large scale population-based study has been done to develop a prognostic nomogram on MFS, but specific prognostic factors associated with treatment regimens and comparison to the behavior of all STS remains unclear [5]. The aim of our study was to characterize demographic and tumor characteristics in a large cohort of patients diagnosed with appendicular MFS and determine how specific epidemiology and survival factors compare to all STS.

Materials and methods

A retrospective review of patients diagnosed with MFS was done in the Surveillance, Epidemiology, and End Results (SEER) database, released in April 2021. SEER reports incidence, population, and survival data on over 8.2 million patients with cancer collected from 18 registries across the nation from the years 1973 to 2020 and is updated annually [6]. For each individual patient with cancer, data are collected by SEER regarding demographics, cancer characteristics, tumor characteristics at the time of diagnosis, treatment within 4 months of diagnosis, patient survival, and cause of death when applicable [7]. SEER data is considered by the field to be a complete and vigorous reporting system for incidence, prevalence, and treatment response of all types of cancer in the United States [8]. The 18 registries reported by SEER represent 28% of the US population collectively and are determined based on their generalizability to total population demographics.

Cases from January 2000 to December 2015 were analyzed to determine a minimum 5-year survival rate. Patients from the registry with International Classification of Diseases for Oncology, 3rd Edition (ICD-O-3) code 8811/3 were selected for this study. Inclusion criteria included patients with tumors in their extremities found histologically to be MFS. Demographic variables for all patients were recorded including age at diagnosis, year of diagnosis, gender, race, and length of follow-up. Tumor characteristics were extracted from available modifiers and recorded including location, tumor laterality, American Joint Committee on Cancer (AJCC) stage (8th edition), tumor grade, and tumor size. Treatment options included resection, chemotherapy and radiotherapy were also included. Oncological outcomes included presence of metastatic disease at diagnosis, overall survival, and 5-year survival. For comparison to all soft tissue sarcomas, patients were included with the AYA site recode 2008 "Soft Tissue Sarcomas" with exclusion of Kaposi Sarcoma.

All statistical analysis was performed using the statistical software SPSS, version 26. Overall and 5-year survival rates were determined for the entire series; Kaplan-Meier curves were used to analyze overall survival rates. Survival was defined as the time from initial diagnosis to time of patient death. Categorical variables including age, sex, race/ethnicity, primary tumor site, grade, laterality, stage, radiotherapy, chemotherapy, and metastasis were compared using Pearson's Chi-Square test and Cramer V. Cox regression analysis was used to determine hazard ratios (HRs) that compared the risk of death between categorical variables.

Results

Appendicular myxofibrosarcoma cohort

There were 1444 patients with MFS in the extremities that met the inclusion criteria. The median age was 62 years (standard deviation (SD), 19) with 774 (54%) patients being male and 670 (46%) females. Most of the cohort (n = 1009, 70%) was non-Hispanic and white. Mean tumor size was 75 mm (2mm-987mm). The most common tumor grade was grade 3 (613, 42.5%) and the most common stage was stage I (n = 482, 33%). A total of 108 patients had metastasis on diagnosis (7%). A total

of 1,182 patients overall underwent surgical excision (91%), 723 (50%) had radiation, 125 (9%) had chemotherapy, and 95 (7%) had both chemotherapy and radiation (Tab. 1).

Overall survival for the entire MFS series was 79%. Survival at five years was 88%. Age was observed to be a significant factor associated with survivorship. Both patients in the 30-70 year old age group and those in the 70+ age group had an increased risk of death when compared to those under 30, with hazard ratio (HR) =3.63 [95% confidence interval (CI): 1.33–9.89, p = 0.012] for the 30–70 group and HR = 7.49 (95% CI: 2.75–20.38, p < 0.001) for the 70+ group (Fig. 1). Other factors that were associated with lower survival rates included increased stage at diagnosis (HR = 2.13, 95% CI: 1.80–2.51, p < 0.001), higher tumor grade (HR = 2.77, 95% CI: 2.10–3.65, p < 0.001) and the presence of metastasis at diagnosis (HR = 11.06, 95% CI: 7.44–16.45, p < 0.001), see Supplementary File — Figure S1 for visual representation of HRs.

Table 1. Characteristics and survival rate of patients with myxofibrosarcoma (MFS)

	N (%)	Overall survival (%)	Cramer V	p-value
Age [years]			0.136	< 0.001
< 30	113 (8)	97		
30–70	814 (56)	88		
> 70	517 (36)	78		
Sex			0.031	0.626
Female	670 (46)	86		
Male	774 (54)	85		
Race and ethnicity			0.020	0.774
Hispanic	163 (11)	84		
NHAI/AN	11 (1)	75		
NHAPI	119 (8)	85		
Non-Hispanic White	1009 (70)	86		
Non-Hispanic Black	120 (8)	87		
Primary site			0.109	0.004
Upper extremity	485 (34)	89		
Lower extremity	937 (65)	84		
Grade			0.209	< 0.001
1	187 (13)	96		
2	470 (33)	92		
3	613 (42.5)	79		
Laterality			0.056	0.718
Left	737 (51)	86		
Right	691 (48)	85		
Midline	16 (1)	85	–	
Stage			0.267	0.234
I	483 (33)	87		
II	314 (22)	86		
III	272 (19)	82		
IV	54 (4)	83		
Radiotherapy			0.061	0.006
No	723 (50)	88		
Yes	718 (50)	84		

Table 1. Characteristics and survival rate of patients with myxofibrosarcoma (MFS)

	N (%)	Overall survival (%)	Cramer V	p-value
Chemotherapy			0.193	0.197
No	1319 (91)	86		
Yes	125 (9)	82		
Radiation and chemotherapy			0.126	< 0.001
No	1349 (93)	86		
Yes	95 (7)	82		
Metastasis at diagnosis			0.301	< 0.001
No	1333 (84)	88		
Yes	108 (7)	67		
Surgical excision				
Yes	1182(91)	85	0.21	< 0.001
No	117 (9)	70		

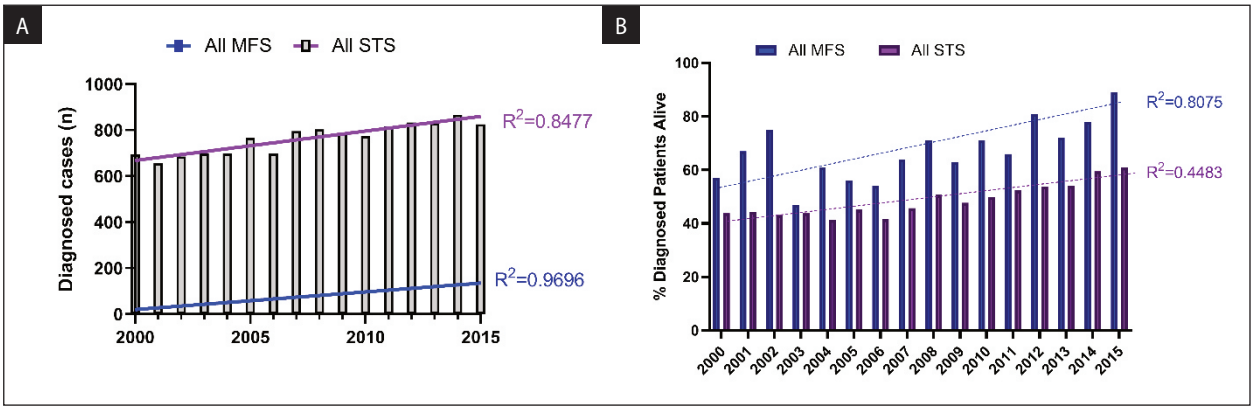

Figure 1. A. New myxofibrosarcoma (MFS) and soft tissue sarcoma (STS) diagnoses made per year for STS (R squared 0.8477, Sy.x 26.68, and $p < 0.001$) and MFS (R squared 0.9696, Sy.x 6.691, $p < 0.001$); **B.** Estimated overall survival per diagnosis year for STS (R squared 0.4483, Sy.x 8.361, $p = 0.0046$) and MFS (R squared 0.8075, Sy.x. 2.778, $p < 0.001$)

Surgical excision was found to decrease the risk of death when compared to non-operative treatment at all stages (HR = 0.21, 95% CI: 0.14–0.32, $p < 0.001$). There were no significant differences in survival when only radiation was used as (neo) adjuvant treatment for all stages. Receiving only chemotherapy was associated with an increased risk of death in patients with tumors diagnosed at stage I (HR = 10.76, 95% CI: 2.47–46.86, $p = 0.002$), stage III (HR = 5.47, 95% CI: 1.55–19.29, $p = 0.008$) and stage IV (HR = 2.71, 95% CI: 0.96–7.60, $p = 0.0059$). Receiving both chemotherapy and radiotherapy was associated with an increased risk of death in patients with cancers at stage I (HR = 5.690, 95% CI: 2.63–12.33, $p < 0.001$) and stage II (HR = 3.34, 95% CI: 1.41–7.94, $p = 0.006$) and in all stages combined (HR = 2.39, 95% CI: 1.6–3.57, $p = 0.012$). See Table 1 for full patient demographics, tumor characteristics, treatment regiments and overall survival for each group, and Supplementary File — Figure S1 for a summary of the HRs associated with individual variables.

Soft tissue sarcoma *vs.* myxofibrosarcoma

When comparing all STS to MFS, there was an increased likelihood to be diagnosed with MFS at older age (MFS = 62 *vs.* STS 56, $p < 0.001$). There was no difference in sex distribution or anatomic primary site. However, there was a significantly higher proportion of MFS diagnoses made between 2008–2015 *vs.* 2000–2007 when compared to

Table 2. Comparison of factors for all soft tissue sarcoma (STS) and myxofibrosarcoma (MFS) from 2000–2015

	MFS N (%)	STS N(%)	p-value
Age [years]			
< 30	113 (7.8)	1645 (13.4)	< 0.001
30–70	817 (56.4)	7406 (60.3)	
> 70	517 (35.8)	3224 (26.3)	
Sex			
F	580 (47)	5582 (45.7)	0.524
M	355 (53)	6639 (54.3)	
Primary site			
Upper	485 (34)	1861 (32.5)	0.645
Lower	937 (65)	3872 (67.5)	
Year of diagnosis			
2000–2007	439 (30.4)	5718 (46.6)	< 0.001
2008–2015	1005 (69.6)	6557 (53.4)	

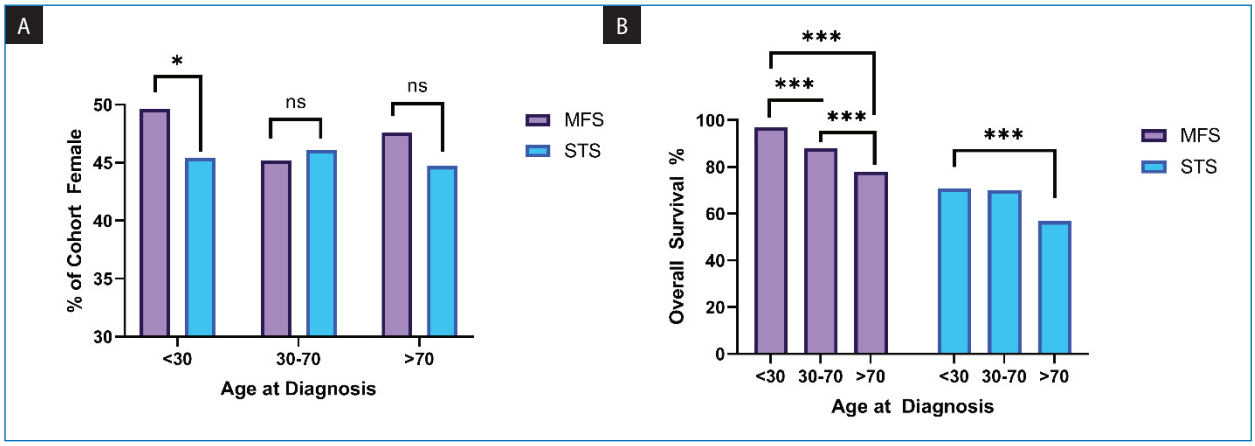

Figure 2. A. Percent of cohort female of each age group with a higher proportion of female patients below the age of 30 being diagnosed with myxofibrosarcoma (MFS) when compared to all soft tissue sarcoma (STS) (49.6% *vs.* 45.4%, p = 0.011); **B.** Significant difference in overall survival for different age groups for MFS (97% *vs.* 88% *vs.* 75%, p < 0.001) and STS (70.9% 70% 56.8%, p < 0.001 for < 30 *vs.* >70 only). See section *Soft tissue sarcoma vs. myxofibrosarcoma* of the main text for hazard ratios

all STS (69.9% of all MFS cases over the 15-year period were diagnosed after 2008 *vs* 53.4% for all STS, p < 0.001) (Tab. 2). The incidence of diagnosed cases of MFS and STS rose from 2000 to 2015, with MFS rising at a higher rate (1.25% increase annually compared to 2.59% increase annually, p < 0.001) (Fig. 1A). At the same time, overall survival increased for patients diagnosed after 2008 for both STS (mean difference 9.4%, p < 0.001) and MFS (mean difference 13.2%, p < 0.001) (Fig. 1B).

Additionally, although there was no significant difference between sex of patients diagnosed with MFS or STS, there was a significantly increased proportion of younger aged patients (< 30) who were female and diagnosed with MFS compared to STS (49.6% *vs.* 45.4%, p = 0.011) (Fig. 2A). As previously mentioned for MFS, those between 30–70 had increased risk of death (HR = 3.63, 95% CI: 1.33–9.89, p = 0.012) and over for those over 70 (HR = 7.49, 95% CI: 2.75–20.38, p < 0.001). For those with STS, only being over 70 was associated with increased risk of death and the HR was not as strongly significant (HR = 3.977, 95% CI: 1.359–10.344, p = 0.017) (Fig. 2B).

Discussion

MFS was found to occur more often in older adults when compared to STS with a patient median age of 62, compared to the median age of STS of 56. This is consistent with what has previously been reported in smaller studies [9–11]. Age was determined to be a significant prognostic factor of survival, and patients under 30 were found to have a very high survival rate.

As HR was monitored for death, we found groups over 70 years of age to be associated with the worst prognosis, with a 53% higher HR than STS as a whole. Clinical data has shown high rates of local relapse in elderly patients with MFS [4] which likely contributes to the worse prognosis in this group. Additionally, both the 30–70 age group and > 70 age groups were associated with worse survival for MFS compared to the > 70 group alone for STS. This indicates that even moderate increases in age may have significant impact on survival outcomes, another contrast with outcomes for STS. Additionally, we saw a higher proportion of female patients diagnosed with MFS under the age of 30 when compared to STS. It has been shown that male patients have a worse prognosis for all STS [12]. Thus, the higher proportion of young female patients diagnosed with MFS could be correlated with the high overall survival of this patient group.

Tumor size at resection, tumor grade, and the presence of metastasis at diagnosis have all been reported as possible prognostic factors [13, 14]. However, as previously noted, past studies have been hampered by inclusion of a broad spectrum of myxoid neoplasms. Our study confirmed that high grade tumors, higher stages, and presence of metastasis at diagnosis were all strongly associated with decreased survival. The reported 5-year survival of MFS reported in small cohort studies has varied widely, from 61% [15] to 82% [16], and overall survival has previously been reported to be approximately 70% [17, 18, 4] but the reliability of these results is impeded due to small sample size, heterogenous treatments, and misdiagnosis of the tumor [10, 19]. One recent study which used MFS data to develop a prognostic nomogram showed 5-year survival of 87.3% similar to our results, although this study did not report overall survival and used a slightly smaller patient sample [5].

There are several treatment methods since the current recommendation is a multidisciplinary approach at sarcoma centers [20]. Surgical resection is the cornerstone in the treatment of STS and this is described as well in patients with MFS. Our study confirmed that surgical excision greatly increases survival. Previous reports have shown mixed benefits of using chemotherapy and/or radiotherapy for MFS [21, 3]. Our study showed no clear evidence that survival improves with either of these treatment options, as we observed that chemotherapy in stage III and IV patients increased risk of death and combined chemo- and radiotherapy increased risk of death for those in stages I and II. There are significant side effects associated with both chemo- and radiotherapy that should be considered. One recent study showed treatment of STS with neoadjuvant radiotherapy is associated with toxicity such as wound healing complications, fibrosis, and lymphedema [22]. Resection and radiation, not chemotherapy, is generally not indicated for early stages of MFS, but chemotherapy may be utilized for large tumors and areas difficult to fully resect such as the head or neck. Difficult to resect tumors may leave positive margins, which increase the risk of death [23] and may be associated with chemotherapy use.

Our results also showed that the sensitivity of MFS to radiotherapy is unclear, given that high-risk tumors will typically receive (neo)adjuvant therapy in addition to resection [3]. The radiosensitivity of MFS has been ambiguous from previous studies as local recurrence and survival rates are similar [3, 16], but more studies need to be done. MFS clinically tends to have lower rates of distant metastasis and higher rates of local recurrence than other types of sarcomas [17].

Additionally, we observed an overall increase in the incidence of both MFS and STS. Other studies have indicated an increase in overall rates of sarcoma, prompting efforts to improve staging and increase rates of surgical resection [24, 25]. To our knowledge, this is the first study to characterize the specific increase in MFS as a subset of STS and demonstrate that they are increasing at a slightly higher rate. This could indicate that diagnostic accuracy of MFS is improving, as they have historically been a diagnostic challenge both clinically and pathologically [19, 10]. Our results also indicated that survival rates for STS and MFS are

increasing over time, with MFS survival increasing at a higher rate, consistent with what has been shown in the literature for STS [26]. To our knowledge, this is the first large scale population study to confirm that survival is increasing for MFS specifically and that it is increasing at a higher rate. This could also be associated with greater awareness of the condition, earlier detection and surgical excision, or new treatment options. including intraoperative radiotherapy, which has shown to promote limb preservation [27].

Limitations of this study include variations in data reporting, migrations of patients in and out of SEER registry areas, and potential selection bias. Potential limitations of the SEER database include that SEER data may represent a younger and more affluent population than the United States in its entirety [8]. Additionally, the SEER population tends to have a higher proportion of foreign-born individuals and urban populations, and over-samples certain racial and ethnic minorities [28]. Another limitation is the lack of information available in the SEER database related to surgical margins. Resection margins have been shown to be an independent factor for overall survival in STS, and this was not controlled for in our analysis [29] [30]. Additional limitations are present due to the heterogenous nature of STS and historically challenging pathology classification [31]. Limitations also exist related to imprecisions in the coding system and eligibility criteria used by SEER. We consider these acceptable limitations as the coding system impacts both study arms and the large sample size available from the SEER database minimizes the impact of misclassifications.

Conclusion

This analysis of the SEER database contributes to the breadth and scope of prognostic data available for clinical decision making in patients diagnosed with MFS. MFS are rare tumors and have historically only been investigated in small groups and studies performed at single institutions. The results of this large-scale analysis provided accurate and generalizable data about 5-year and overall survival rates for MFS. While general survival trends and overall features of MFS have been described in prior studies, no large-scale analysis with comparison to all STS has been available. It is important to monitor changes in patient demographics, outcomes, and prognostic factors for rare malignancies and see how they compare to well characterized conditions to help optimize detection strategies and modify treatment algorithms.

Ethics approval and consent to participate

All patient identifiers are removed from the SEER database; consequently, studies using the SEER database are exempt from Institutional Review Board approval.

Consent for publication

Not applicable,

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Authors' contributions

All authors contributed to the study design, data collection, data analysis, and reporting for this manuscript. All authors have read and approved the final submitted manuscript.

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