Advances in Radiation Oncology (2024) 9, 101485

advances in radiation oncology

www.advancesradonc.org

Scientific Article

Myxofibrosarcoma: Outcomes, Prognostic Factors, and Role of Neoadjuvant Radiation Therapy

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Received 21 September 2023; accepted 25 February 2024

Purpose: Myxofibrosarcoma (MFS) is a subtype of soft tissue sarcoma with a highly infiltrative growth pattern that leads to a higher risk of inadvertent positive surgical margins and local relapse. Poorly defined tumor margins also pose a challenge for radiation therapy (RT) planning, in terms of treatment volumes and administration of pre- versus postoperative RT. This study aims to evaluate local control and patterns of recurrence in patients with MFS treated with neoadjuvant RT followed by definitive surgical excision.

Methods and Materials: Multiple institutional databases were retrospectively searched for patients diagnosed with MFS between 2013 and 2021 who were exclusively treated with preoperative RT followed by definitive surgery at our institution. The endpoints of the study were defined as local tumor recurrence, distant metastasis, and death after the date of definitive surgery.

Results: Forty-nine patients met the inclusion criteria and were included in the final study. The median age at diagnosis was 67 years, and 71% of patients were male. The tumor was superficially located in 63% of patients, and the mean tumor size at presentation was 7.8 cm. All patients received neoadjuvant RT and completed their planned course of treatment. Neoadjuvant chemotherapy was administered in 22% of patients. Inadvertent excision (IE) before definitive treatment was performed in 25 patients (51%), 84% of which had superficially located tumors. All margins were assessed using frozen section analysis at the time of definitive surgery, and 100% of patients had negative surgical margins, with 25% having no residual tumor. With a median follow-up of 4.7 years, the 5-year local control rate was 87%, and 5-year overall survival was 98%. Tumor depth was associated with distant metastasis ($P < .01$).

Conclusions: Despite the infiltrative nature of MFS, preoperative RT followed by definitive surgical excision, especially in the setting of a reliable frozen section margin analysis, was associated with excellent local control.

Introduction

Myxofibrosarcoma (MFS) is a soft tissue sarcoma (STS) subtype, previously known as a myxoid variant of malignant fibrous histiocytoma (MFH).[1] The World

Sources of support: This work had no specific funding.

Research data are stored in an institutional repository and will be shared upon request to the corresponding author.

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https://doi.org/10.1016/j.adro.2024.101485

Health Organization first defined MFS as a discrete entity of fibroblastic tumors, separate from MFH, in 2002.[2] MFS most commonly presents in the extremities of adults[3] and represents about 5% of STS diagnoses.[4] MFS tends to be superficially located (64%-87%)[5-7] and exhibits an infiltrative growth pattern that correlates with a multidirectional T2 signal extension on magnetic resonance imaging (MRI), often spreading along the fascial plane and creating what is called a "tail sign".[4] However, focal growth patterns on MRI can also be seen in these infiltrative tumors, making it difficult to correctly evaluate the extension of the tumor preoperatively.[8] Furthermore, the infiltrative tumor borders can be dismissed as peritumor edema on pretreatment MRI, leading to inadequate resections and higher rates of local recurrence.[9] This makes MFS more challenging to treat when it comes to radiation therapy (RT) planning and often leads to larger RT volumes, which are used in an attempt to encompass all the microscopic extensions of the tumor.[10] In extremity and truncal STS, preoperative external beam radiation therapy (EBRT) is preferred, given its better ability to define gross disease, lower prescription doses, and lower rates of late toxicities.[11] However, the ill-defined histologic margins of MFS make it more difficult to determine the appropriate timing of EBRT in these patients, with some institutions preferring to use RT postoperatively after resection margins have been confirmed upon final pathology review.[12-14]

The infiltrative nature of MFS is also correlated with a higher incidence of positive surgical margins; that, along with higher tumor grade, increases the risk of multiple recurrences, limb amputation, distant metastasis (DM), and/or disease-related death.[8,10,15-17] Thus, a well-planned wide resection of the tumor is essential in the management of MFS. Unfortunately, unplanned non-oncological excisions are common in superficially located STSs, including MFS.[18]

The purpose of this study was to evaluate whether preoperative RT with frozen section pathology margin assessment can be used to achieve good local control (LC), despite the infiltrative nature of MFS. We evaluated LC, patterns of recurrence, and survival rates in patients with MFS treated with neoadjuvant RT followed by definitive surgery. Potential prognostic factors, including tumor histology, size, role of inadvertent excision (IE), and location, were assessed. In addition, the rate of reconstructive surgery associated with preoperative RT is reported. The rarity of this particular histology and its unique behavior among STSs makes a review of this small, consecutively treated patient population a valuable addition for understanding appropriate MFS management strategies.

Methods and Materials

This retrospective study was approved by our institutional review board. The institutional radiation oncology database was searched for patients with MFS who received RT and definitive surgery at Mayo Clinic Rochester between 2013 and 2021. The institutional pathology database was then also searched for patients who received an MFS diagnosis in the same time frame, and the 2 lists were compared to identify duplicate cases before combining. Patients who received only adjuvant RT or no RT and those who did not have their definitive surgical resection at our institution were excluded from the study. Medical records, radiographic imaging, and pathologic reports of patients were searched to gather clinicopathologic data on tumor size, depth, and grade; surgery margins; postoperative course; RT and chemotherapy treatment courses; and long-term outcomes.

All patients at our institution were treated by a dedicated sarcoma team, including a dedicated sarcoma radiation oncologist, orthopedic oncology surgeon, and medical oncologist. Patient management was discussed by the dedicated multidisciplinary team before treatment initiation.

Standard frozen section analysis of surgical margins was performed on all patients at the time of definitive surgery. Margin status was considered negative if the inked resection margins had no neoplastic malignant cells. Intraoperative margin analysis was considered accurate if it corresponded with the final pathology report. The distance of the tumor to the nearest resection margin was noted. Furthermore, all pathology records from definitive surgery were re-reviewed by a sarcoma pathologist (JJT) for grading, margins, tumor viability, and treatment effect data. The histologic grading from grades 1 to 3 was based on the French Federation of Cancer Center Sarcoma Group, which takes tumor differentiation, mitotic count, and necrosis into consideration.

Tumor location was classified as proximal and distal upper extremity relative to the elbow joint, proximal and distal lower extremity relative to the knee joint, or trunk for tumors located proximal to the shoulder and acetabulofemoral joints.

Tumor depth was classified as deep versus superficial based on the tumor epicenter being superficial or deep to the muscle fascia. That was determined using the imaging records at the time of presentation.

Tumor size was calculated from imaging records at the time of presentation, plus the size of any inadvertently excised mass as applicable.

The AJCC 8th Edition Staging System for Soft Tissue Sarcomas[19] was used to stage all patients using the tumor size and grade as obtained from radiographic imaging and pathology reports, respectively.

In preparation for RT, all patients underwent simulation with computed tomography (CT) imaging in treatment position. For the majority of patients, an MRI in treatment position was also obtained. Various immobilization devices were used, both during simulation and daily treatments, based on the target treatment field,

including but not limited to Vac-Lok for proximally located tumors and Aquaplast Thermoplastic for more distally located ones. On-board imaging with x-rays (using bony landmarks) and/or cone beam CT were used to verify the patient's positioning daily. RT was administered using either 3-dimensional conformal RT or intensity modulated RT, and appropriate dose constraints were used for bone, soft tissue, and/or intrathoracic organs based on tumor anatomic location. For patients with intact tumors at presentation, the treatment field routinely covered a gross tumor volume (GTV), a clinical target volume (CTV), and a 0.5 cm planning target volume expansion. CTV was defined following the Radiation Therapy Oncology Group atlas guidelines for primary STSs[20] and routinely included a 3.0 cm radial expansion of GTV in the subcutaneous compartment with a 0.5 cm expansion into the underlying muscular compartment. In patients who had undergone IE before treatment, a deeper CTV expansion was applied when the fascial layer was disrupted during surgery. Additionally, for those patients, radiopaque markers were placed on the surgical scar during simulation, and the treatment field routinely included tissue deeper to the scar. A decision on whether to cover the scar tissue with a bolus depended on the surgical plans for skin removal and was made through a discussion with the orthopedic surgery team.

Local recurrence (LR), distant metastasis (DM), and overall survival (OS) were defined from the date of definitive surgery and assessed using Kaplan−Meier methods, with LR defined as any pathologically or radiographically confirmed evidence of disease within the radiation or surgical field or in the immediately surrounding region.[21] Log-rank tests and Cox proportional hazard models were used to investigate factors associated with outcomes. Statistical significance was defined as $P < .05$ for all tests.

Results

A total of 49 patients met our inclusion criteria and were included in the final study. Demographic and tumor characteristics are shown in Table 1. Most patients were male (71%), the majority had superficial tumors (63%), and the most common location was the lower extremity (45%). More than half of the patients (51%) presented after undergoing anIE. Tumor diameter was not available in one patient with IE. Most tumors were more than 5 cm in diameter (67%). Grading information was available for 45 patients, with 35 tumors (78%) documented as grade 3. Following the AJCC 8th Edition Staging System for Soft Tissue Sarcomas,[19] all cases were staged at presentation except for 2, owing to incomplete grade and/or size data. The majority of patients, 33 (70%), presented with stage IIIA/IIB.

All patients completed neoadjuvant RT, with 47 receiving the standard 45 or 50 Gy in 25 fractions. Two patients

Table 1 Patient demographics and tumor characteristics, treatment modalities, and timeline

	Overall (N = 49)
Age at diagnosis, years	
- Median (Range)	67 (40-89)
Sex	
- Female	14 (29%)
- Male	35 (71%)
Location	
- Proximal UE	9 (18%)
- Distal UE	5 (10%)
- Proximal LE	12 (25%)
- Distal LE	10 (20%)
- Trunk	13 (27%)
Depth	
- Deep	18 (37%)
- Sup	31 (63%)
Tumor diameter (cm)	
- Number missing	1
- Mean (SD)	7.8 (5)
- Median (Range)	6.3 (1.4, 24.0)
Grade	
- Indeterminate	4
- 3	35 (78%)
- 2	6 (13%)
- 1	4 (9%)
Stage	
- Indeterminate	2
- IA	3 (6%)
- IB	1 (2%)
- II	10 (21%)
- IIIA	26 (55%)
- IIIB	7 (15%)
Inadvertent excision	
- No	24 (49%)
- Yes	25 (51%)
Radiation therapy	49 (100%)
Timeline	
- Preoperative	40 (82%)
- Preoperative with chemotherapy	9 (18%)
Dose (Gy)/Fractionation	
- 42.75/15	2 (4%)
- 45.00/25	1 (2%)

(*continued on next page*)

Table 1 (*Continued*)

	Overall (N = 49)
- 50.00/25	46 (94%)
Chemotherapy	11 (22%)
Timeline	
- Preoperative before RT	2 (4%)
- Preoperative concurrent with RT	4 (8%)
- Both	5 (10%)
Excised tumor size (cm)	
- No residual tumor	12
- Mean (SD)	6.4 (5.0)
- Median (Range)	5.0 (0.0, 23.0)
Closest margin (cm)	
- No residual tumor	12
- Mean (SD)	1.0 (1.3)
- Median (Range)	0.7 (0.1, 6.1)
Reconstructive surgery	
- No	1 (2%)
- Yes	48 (98%)

Abbreviations: LE = lower extremity; RT = radiation therapy; SD = standard deviation; Sup = Superficial; UE = upper extremity.

had a hypofractionated course, with 42.75 Gy given over 15 fractions in an institutional study (clinical trial ID# NCT04562480). Care was taken when defining the RT volumes to include any MRI T2 signal that extended beyond the gross disease or in the surgical bed for patients presenting after IE. In addition to preoperative RT, 2 patients received intraoperative radiation (11 and 10 Gy respectively), and 1 patient received 16 Gy in 4 fractions of postop brachytherapy administered for close surgical margins. Eleven (22%) patients received neoadjuvant chemotherapy in addition to RT: 2 before radiation, 4 concurrent with radiation, and 5 both prior to and concurrent with radiation (Table 1). Different systemic therapy regimens were used, including doxorubicin with ifosfamide and methotrexate, doxorubicin, and cisplatin, among others.

Twenty-five (51%) patients had a history of IE before definitive treatment. In these cases, 84% of tumors were superficially located, and 78% were grade 3. The surgical margins at the time of IE were positive in 76% of patients, with 6 outside cases having an unknown margin status.

All patients underwent surgical excision with the goal to acheive a negative margin. The median time between the neoadjuvant RT end date and definitive surgery was 35 days (range, 17, 66). Surgical margins by frozen section were negative in all patients, with 12 having no residual tumor after IE and neoadjuvant treatment. Frozen section margins were all confirmed by permanent section. In one case, initial periosteal margins were positive by frozen section. Additional tissue was excised, and the tumor bed was boosted with perioperative brachytherapy (16 Gy in 4 fractions). In patients where a residual tumor was identified, the median excised tumor diameter was 5.0 cm (range, 0.0, 23.0), with a closest margin median of 0.7 cm (range, 0.1, 6.1) (Table 1). The median viable tumor percentage as per pathology review was 50% (range, 0%-100%). Some of the treatment effects reported by pathology were fibrosis, hyalinization, and granulomatous reaction within the tumor bed. Nearly all cases (98%) required reconstructive surgery for wound closure (100% in patients after IE). This included complex wound closure and skin grafting, with/without flap surgery.

With a median follow-up in survivors of 4.7 years, the 2-year and 5-year progression-free survival (PFS) rates were 89% and 73%, respectively, and the 5-year OS was 98% (Fig. 1). The 5-year LC was 87%. By the last follow-up, 5 (10%) patients developed LR, while 7 (14%) had DM. The most common site of DM was the lung (4/7, 57%) followed by bone (2/7, 29%). Table 2 shows the tumor characteristics and status of patients who developed LR. All patients who developed LR were treated with standard fractionation neoadjuvant RT at presentation. Out of the 5 patients who had LR, 2 (40%) also developed DM at 11 and 18 months following the first recurrence, respectively. Out of the 5 patients, 4 (80%) were alive with no evidence of disease at the last follow-up, and all 5 were alive at the last contact. Initial LR was managed with local re-excision in all cases but 1, supplemented by RT in 3 cases. One patient with LR was treated with stereotactic body RT. A total of 3 out of 5 cases had multiple subsequent recurrences that were managed with different treatment modalities, including surgical resection, cryoablation, and/or RT. The LR rate in patients who had IE was 3 out of 25 (12%) versus 2 out of 24 (8%) in patients who did not. DM occurred in 1 out of 25 patients (4%) who had IE, compared with 6 out of 24 (25%) in patients who did not (Table E1). Log-rank tests showed no statistically significant difference in outcomes associated with IE (P = .60, 0.05, 0.19, and 0.20 for LR, DM, PFS, and OS, respectively).

The rate of DM was associated with tumor depth. Deep tumors were associated with an increased likelihood of DM, compared with superficial tumors ($P < 0.05$) (Fig. 2). However, depth was not associated with LR or OS (P = .25 and .09, respectively) (Table E2).

Cox proportional hazard models were fitted to investigate relationships between tumor size and outcomes. Tumor diameter had no association with the risk of LR, DM, disease progression, or death (P = .77, .12, .19, and .49, respectively) (Table E2).

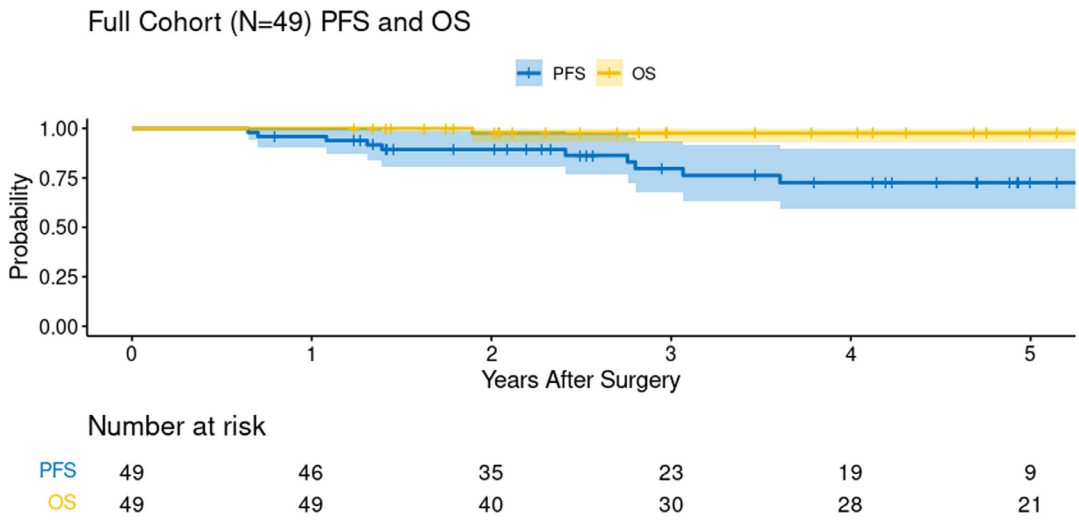

Figure 1 Overall survival and progression-free survival Kaplan−Meier estimates.

Discussion

Neoadjuvant RT has several theoretical benefits over adjuvant RT in the treatment of STS, including its provision of the ability to plan treatment more accurately, owing to a better definition of GTV, minimization of dose-limiting toxicity, a lower total dose, and potentially increased chances of a complete tumor removal.[11] However, given the infiltrative nature of MFS and ill-defined margins on imaging, the preferred timing for EBRT in these patients is less clear, with some institutions preferring initial surgery to ensure negative surgical margins.[14] In the current study, we endeavored to define the outcome of neoadjuvant RT followed by definitive excision in patients with MFS in terms of LC and OS. To the best of our knowledge, this is the first retrospective study evaluating the outcomes of MFS patients treated exclusively with neoadjuvant RT followed by definitive surgery.

With a median follow-up of 5 years, our LR rate of 10.2% indicates excellent LC using the combination of neoadjuvant RT followed by R0 surgical resections, compared with the LR rates reported in the literature, summarized in Table 3. Out of the summarized studies, only 2 focused solely on patients who underwent RT; however, both studies exclusively involved superficial MFS.[13,14]

A total of 2 out of 5 LR cases had close surgical margins at the time of definitive surgery (≤ 0.1 cm). Hasley et al.[23], in their study of surgical margins in extremity sarcoma, found that R0 resections with close margins (< 0.1 cm) had a high recurrence rate, similar to that of intralesional resections, and narrow margins may especially be of concern in this particular histopathology. Other studies have also reported the prognostic utility of surgical margin status for MFS local control and recurrence risk.[17,24] On the other hand, Gundle et al,[25] in their work on margin classifications for STS resection, found that close surgical margins (< 1 mm) may be adequate in mitigating the risk for LR with multi-modality treatment. In our study, owing to the small sample size, we were not able to assess the impact of close surgical margins on LR risk with an acceptable level of confidence.

Table 2 Summary of local recurrence cases

Site	Depth	Size (cm)	Grade	Stage	DS closest margin (cm)	Time to LR (mo)	DM	Status	LR to FU time (mo)
T	Sup	7.5	3	IIIA	1	41	N/A	ANED	58
UE	Deep	13	3	IIIB	Close (≤ 0.1)	16	Bone L3	ANED	65
UE	Sup	5.5	Unknown	IIIA	0.1	17	N/A	ANED	4
T	Deep	Unknown	Unknown	Unknown	6.1	8	Abdomen	AWD	17
T	Deep	8.6	2	IIIA	N/A	33	N/A	ANED	8

Abbreviations: ANED = alive with no evidence of disease; AWD = alive with disease; DM = distant metastasis; DS = definitive surgery; LR = local recurrence; LR to FU = time from local recurrence to last follow-up; Sup = superficial; T = trunk; UE = upper extremity.

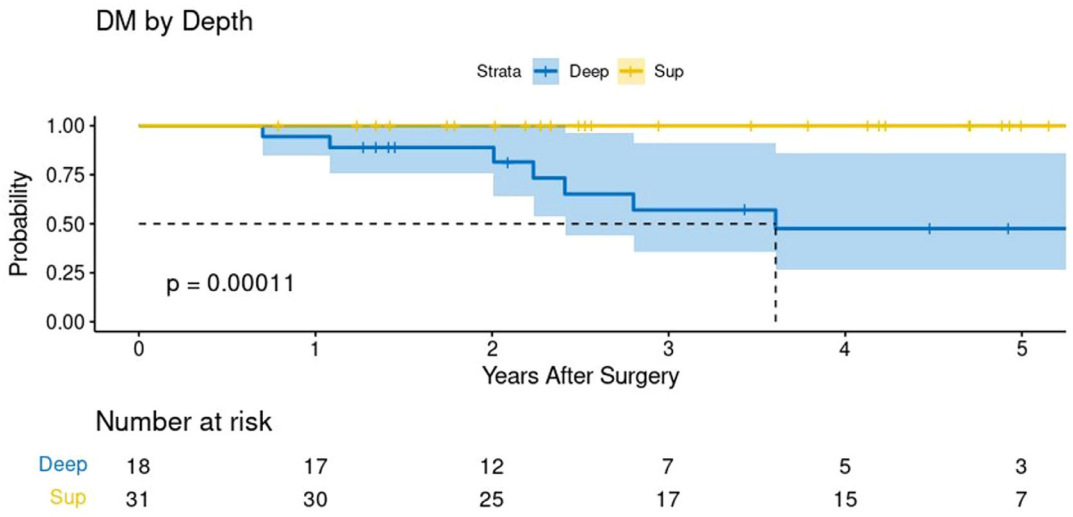

Figure 2 Distant metastasis-free survival for patients with superficial versus deep-seated tumors.

Fourman et al,[14] in their work on superficial MFS, found that temporizing the excised tumor bed with a wound VAC until final margins were achieved can be performed to achieve a better LC than that associated with a single-stage excision/reconstruction approach. However, in our cohort, standard frozen section analysis of surgical margins was performed on all patients, and with a 97.8% accuracy (with only a 0.1% rate of clinically significant errors),[26] it safely eliminated the need for a staged surgical technique.

Pathologic response to preoperative RT in MFS has not been associated with outcome. Allignet et al,[27] in their study looking at neoadjuvant RT treatment response across 4 different STS histologic subtypes, reported poor treatment response in the MFS subtype group, with a median residual viable tumor of 60% (interquartile range, 30%-80%) after RT, with only 10% necrosis. Likewise, Shaefer et al,[28] in their investigation of the histologic appearance of STS after preoperative RT, found that the pathologic response rates for STSs are relatively low. Their MFS sample, which constituted 25% of the population, had a 30% (10-100) median residual viable tumor with a median RT dose of 50 Gy (range, 50-59.5). This is only a slightly higher treatment response compared with our observed median viable tumor percentage of 50% (0-100) with comparable treatment doses. For their MFS subpopulation, they reported a 5-year recurrence-free survival of 76% and a 5-year OS of 86%. We had comparable

Table 3 Myxofibrosarcoma local recurrence rates as reported in literature

Current Study	Sample size 49	LR rate (%) 10	Median follow-up (yr) 4.7	% receiving RT 100%	RT approach 100% preoperative
Look Hong et al. 2013[17]	69	16	3.4	77%	60% Preoperative 15% Postoperative 25% Both pre and postoperative
Haglund et al. 2012[16]	36	31	3.5	78%	18% Preoperative 68% Postoperative 14% Both pre and postoperative
Fourman et al. 2021[14]	53	19	3.8	100%	Either preoperative or postoperative. Exact percentages not reported
Sanfilippo et al. 2011[22]	158	17	4.4	51%	Not reported
Ghazala et al. 2016 [12]	50	14	Not reported	74%	100% postoperative, 1 case with brachytherapy.
Riouallon et al. 2012[13]	21	57	Not reported	100%	100% postoperative

Abbreviations: LR = local recurrence; RT = radiation therapy.

Table 4 Myxofibrosarcoma long-term outcomes as reported in literature

Current Study	Sample size 49	5-yr LC % 87	5-yr DMFS % 80	5-yr PFS % 73	5-yr OS% 98
Shaefer el al. 2017[28]	25	Not reported	Not reported	76	86
Kikuta et al. 2013[5]	100	74.8	Not reported	Not reported	Not reported
Look Hong et al. 2013[17]	69	72	82	Not reported	61
Boughzala-Bennadji et al. 2018[24]	425	67	83	Not reported	80
Sambri et al. 2016[29]	129	74	76	Not reported	Not reported

Abbreviations: DMFS = distant metastasis-free survival; LC = local control; OS = overall survival; PFS = progression-free survival.

outcomes in our cohort, 73% for 5-year PFS and 98% for 5-year OS, despite the lower treatment response. The cumulative data in the literature, including this series, supports the lack of correlation between tumor response and disease outcomes.

Table 4 summarizes reported outcomes of MFS across different studies; with a 5-year LC of 87%, 5-year PFS of 73%, and 5-year OS of 98%, our study shows excellent survival outcomes with the use of neoadjuvant RT followed by definitive resection.

All patients who had disease progression (LR, DM, or both) presented with stage IIIA or IIIB tumors. Previous studies have also identified high tumor grade and high mitotic rate to be prognostic factors for worse survival in MFS.[30,31] Our results showed no difference in LC or OS between the patients who underwent IE before presentation and those who did not. This is consistent with several earlier studies on the impact of nononcological excisions, which reported that IE of STS does not negatively impact oncological outcomes. However, they all reported that it results in the need for additional reconstructive surgery and has a negative impact on patient-reported outcomes. We found reconstruction surgery common in this population overall, likely related to the subcutaneous location as the dominant site for this histology. These studies have also established that aggressive re-excision and multidisciplinary treatment can mitigate the unfavorable clinical course resulting from the high incidence of residual tumor after the initial IE.[32-34]

In our series, deeply seated tumors were associated with a higher rate of DM, which did not translate into a change in OS. Mentzel et al[6] have previously reported similar findings. They found that deeply located tumors were associated with a higher incidence of DM; however, their work also showed an associated increase in tumor-related death. The lack of association in our findings might be due to the small sample size.

Our study had a few limitations related to its retrospective nature, including selection biases and missing or incomplete data. Our main objectives were to examine the role of neoadjuvant RT in LC and OS in patients with MFS and to assess the rate and impact of nononcological surgeries, surgical outcomes, and the potential impact of preoperative RT on recovery. However, not surprisingly, there was incomplete data on IEs performed at outside facilities, which led to incomplete staging information in some cases. In terms of institutional records, we were not able to determine precise descriptions of the surgical procedures performed during definitive excisions and/or reconstructive surgeries, descriptions of reoperations, or rates of wound complications. For example, the rationale for different reconstructive operations was not always clear. Other limitations included a limited number of cases with which to evaluate the impact of neoadjuvant chemotherapy in combination with neoadjuvant RT. However, despite the small sample size of 49, this is considered a substantial number for a single-institution series of a rare tumor such as MFS.

In summary, despite the infiltrative nature of MFS, neoadjuvant RT can still lead to good LC outcomes. This may be due to the ability to sterilize small-volume disease at the periphery of this infiltrative process. In addition, centers that have access to reliable frozen section margin analysis can use this technology to improve the accuracy of their surgical margin assessment and further increase the chances of successful treatment. Based on our findings, neoadjuvant RT with 45 to 50 Gy standard fractionation followed by complete resection seems to be associated with excellent LC for MFS. Further research is necessary to assess the effectiveness of a hypofractionated course.

Disclosures

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.adro.2024.101485.

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