ANTICANCER RESEARCH *40*: 5793-5800 (2020)
doi:10.21873/anticanres.14596

Preoperative Evaluation of Myxofibrosarcoma: Prognostic Value and Reproducibility of Different Features on MRI

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Abstract. *Background/Aim: Myxofibrosarcoma (MFS) is characterized by an infiltrative growth pattern. This study aimed to determine the correlation between overall survival (OS) and morphological features of MFS as well as examine the reproducibility of these findings on preoperative magnetic resonance imaging (MRI). Patients and Methods: Fifty-eight MFS patients underwent preoperative MR imaging with the following features analysed: i) tumour size, ii) localization, iii) margins, iv) morphology, v) signal characteristics, vi) contrast enhancement, vii) presence and extent of perilesional oedema, and viii) presence of the tail sign. Results: Only circumscribed perilesional oedema was associated with a significantly better survival compared to diffuse oedema (p=0.010), which was found in the majority of cases. The tail sign was found in less than 50% of the cases. Cohen's kappa coefficients confirmed a relatively high interrater variability. Conclusion: Perilesional diffuse oedema on MR imaging of MFS is significantly correlated with a poor overall survival. The interrater variability in interpretation of MR examinations varies from slight to substantial agreement. Preoperative MR imaging with detailed planning of the resection seem to be a logical approach to achieve negative resection margins and recurrence-free survival.*

Myxofibrosarcoma (MFS) was first described as a sub-entity of sarcoma in the 1970s by Angervall *et al*. and was recognized as an independent disease by the World Health Organization (WHO) in 2002. Currently, MFS is considered among the most common types of soft tissue sarcoma in the extremities (1); however, soft tissue sarcoma in general is a rare disease with an annual incidence of approximately 2-5 per 100,000 per year, and MFS represents approximately 20% of all soft tissue sarcomas (2).

MFS presents as a deep or subcutaneous round or oval mass similar to other soft tissue sarcomas (3). The gold standard treatment for MFS is surgical resection with histologically negative margins, which results in superior clinical outcomes compared to radiotherapy and/or chemotherapy alone (4). Negative margins after the first surgery are sometimes difficult to obtain because, compared to other soft tissue sarcomas, MFS can stand out with special growth patterns, such as the lack of a pseudocapsule and infiltrative growth along the fascial planes (5, 6).

It is clear that precise planning prior to the operation is necessary for surgeries intending to achieve a wide tumour resection. As a special feature of this tumour entity, magnetic resonance imaging (MRI) often shows an infiltrative growth with spread along the muscle fascia, which complicates the planning of the operation. In contrast to other soft tissue sarcomas, the surgical planning of MFS resection has to include not only the central mass but also the pattern of extension along fascial structures (7).

This spreading pattern may result in higher recurrence rates of MFS compared to other soft tissue sarcomas, such as liposarcoma (8). In particular, infiltrative growth can give a false impression of tumour-free margins intraoperatively, but microscopic extensions in the surrounding tissue lead to a positive histopathological tumour margin (3). As expected, meeting the target of negative margins in the initial operation is of tremendous importance for long-term survival (9).

MR imaging is the gold standard for the preoperative planning of wide resection. T1-weighted, T2-weighted and

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Key Words: Myxofibrosarcoma, MR imaging, reproducibility, prognosis, survival.

contrast-enhanced MR sequences are standard and commonly used by radiologists in sarcoma centres (10). Planning resection based on MRI is one of the most important steps before the operation. Interdisciplinary cooperation between members of different expertise, such as radiologists, pathologists and surgeons, at tertiary referral centres seems to be logical for achieving good long-term survival as already partially shown for the treatment of Ewing sarcoma (11).

Previous studies have addressed the computed tomography (CT) and MRI patterns in cohorts of MFS patients and their correlation with survival (12-14). To the best of our knowledge, no studies have addressed the interrater variability in the assessment of preoperative MRI examinations in a large cohort of MFS patients and correlated the findings with the overall prognosis.

Therefore, this study aimed to determine the correlation between overall survival (OS) and the morphological features of MFS as well as assess the reproducibility of these findings on preoperative MR imaging.

Patients and Methods

The Institutional Review Board (IRB) of the Klinikum rechts der Isar approved the study (Faculty of Medicine, Technical University Munich, 441/16), and all investigations were conducted according to ethical principles of declaration of Helsinki. A written informed consent was obtained from all patients included in the study.

The clinical data of patients treated for MFS in our institutional database (Klinikum rechts der Isar, Technical University Munich, Germany) between January 2010 to December 2017 were retrospectively evaluated. The inclusion criteria were as follows: i) histopathologically proven MFS confirmed by two experienced skeletal pathologists, based on the WHO classification of soft tissue tumours; ii) tumour localized in the trunk or the extremities; iii) preoperative MRI examination following a standardized protocol only at our institution; and iv) surgical therapy at our clinic. In 7 patients, the preoperative MRI images were not considered sufficient for further analysis because they were not performed at our clinic and were of inadequate image quality.

We recorded the i) age (at the time of diagnosis), ii) gender, iii) localization, iv) tumour margin status [R0: negative/clear margins, R1: positive/involved margins (microscopic), R2: positive/involved margins (macroscopic), and Rx: inability to assess the presence of residual tumour], v) survival, vi) local recurrence, vii) metastasis, and viii) duration of follow-op (months from diagnosis).

All patients underwent preoperative MRI examinations using a 1.5 Tesla (T) (Magnetom Avanto, Siemens Medical Solutions, Erlangen, Germany; Gyroscan NT Intera, Philips Medical Systems, Best, the Netherlands) or a 3.0 T (Magnetom Verio; Siemens Medical Solutions) system. Depending on the localization of the sarcoma, dedicated surface coils were used. MR images were assessed independently by two radiologists with 25 years and 7 years of experience in musculoskeletal radiology. The readers were blinded to the detailed histological diagnosis and other clinical information. The image material was presented in a random order. The following radiological parameters were assessed: i) tumour size (cm), ii) localization (epifascial, subfascial, or epi- and subfascial), iii) tumour morphology (multinodular, *i.e.*, more than one separate mass in the same region, mass-like, *i.e.*, round or oval mass, or with superficial spreading extending longitudinally in subcutaneous tissue), iv) tumour margins (well-defined or infiltrative), v) contrast enhancement (extent of enhancement <1/3, 1/3-2/3, or >2/3 of the tumour volume), vi) presence of perilesional oedema (yes/no), vii) extent of oedema (diffuse or circumscribed), and viii) the tail sign (defined as a well-defined, sharp or tapering pointed curvilinear projection at least 1.0 cm in length of a high T1 signal after contrast administration yes/no).

Table I. *Interpretation of Kappa values (15).*

Kappa value	Agreement
<0.0	Poor
0.00-0.20	Slight
0.21-0.40	Fair
0.41-0.60	Moderate
0.61-0.80	Substantial
0.81-0.99	Almost perfect

The scans were performed within 6 weeks before surgery for the preoperative planning. The operative resection planning included complex anatomical overall planning considering the axial T2 sequences and coronal or sagittal T1 sequences before and after the intravenous injection of Gadolinium (Gd).

The resection of MFS was carried out as a wide resection, taking into account the zone of perilesional oedema and contrast enhancement.

The data were analysed using SPSS 22.0 (IBM, Armonk, NY, USA) and the free software R version 3.6.1 (The R Foundation for Statistical Computing, Vienna, Austria). The quantitative results obtained by both readers are shown in percentages. The agreement between the two readers was assessed using the kappa statistic in Table I [Cohen's kappa (κ) coefficient (15)]. For the survival analysis, the Kaplan-Meier method was used. To test for associations between potential prognostic factors and mortality, the log-rank-test (Mantel-Cox) was used.

Results

We retrospectively identified 58 patients (male/female, 35/23) with a median age of 62.5 years (range=26-91 years), and a minimum of 30 months follow-up period of the survivors (range=30-109 months). Forty-six patients had MFS located in a lower extremity, 10 patients had MFS located in an upper extremity and 2 patients had MFS located in the chest wall. The mean tumour size (longitudinal/axial plane) was 11.0 cm × 7.6 cm (range=7.2-14.9 cm/6.2-9.0 cm).

The radiological variables were analysed in terms of their potential significance for patient survival. The expertise of the radiologist with the most professional experience (25 years) was used as the basis for this evaluation. The detection of the tail sign had no effect on OS (p=0.667,

Figure 1). The presentation of perilesional oedema in detail correlated with OS as follows: the patients with circumscribed oedema showed significantly better survival than the patients with diffuse oedema (p=0.010, Figure 2), while the presence of perilesional oedema alone had no influence on survival (p=0.966). The hazard ratio (HR) of overall survival in the presence of circumscribed oedema as compared to diffuse oedema was 9.3 [95% confidence interval (CI): 1.2-76.2, p=0.037). In a further subgroup analysis of patients with diffuse (n=27) or circumscribed perilesional oedema (n=27), the tumour margins were analysed. Negative margins (R0) were detected in 17 of the 27 patients (63.0%) in both subgroups with oedema. Eight patients (29.6%) with diffuse oedema and six patients (22.2%) with circumscribed oedema were classified as R1, while two patients (7.4%) and four patients (14.8%) were classified as Rx, respectively. In the subgroup analysis, 5 patients with diffuse oedema and 4 patients with circumscribed oedema showed local recurrence. However, further statistical evaluation of the difference between the tumour margins and local recurrence depending on the type of oedema, such as the hazard ratio, were not possible due to the small number of events. Sixteen patients in the group with diffuse oedema and 5 patients with circumscribed oedema developed distant metastases. The hazard ratio of overall survival in the presence of metastases was 4.9 (95%CI=0.6-39.7, p=0.139). Concerning the difference in the type of oedema, further statistical analyses were not useful due to the small number of events. Additionally, the MRI morphology of the tumour margin (p=0.966, Figure 3), the tumour localization (p=0.312, Figure 4), the tumour morphology (p=0.478) and the extent of Gd enhancement (p=0.477) showed no association to patient survival.

Despite the presence of highly qualified skeletal radiologists, the examined variables showed variance. The sarcoma was epifascial in almost 20% of the patients (reader range=17.2-17.3%), subfascial in approximately 60% of the patients (reader range=58.6-69.0%), and epifascial and subfascial in the remaining patients (reader range=13.8-24.1%). The radiological finding of whether the tumour appearance was i) multinodular, ii) mass-like (round/oval) or iii) with superficial spreading, showed a range of results [reader range: i) multinodular (15.5-39.7%), ii) mass-like (56.9-75.9%) and iii) with superficial spreading (3.4-8.6%)]. Concerning the tumour margin, approximately half of the cases showed well-defined (reader range=53.5-55.2%) or diffuse infiltrative growth (reader range=44.8-46.5%). Analogous to approximately half of the cases, the tumour showed Gd enhancement in more than 2/3 of the tumour volume (reader range=50.0-55.2%), while less than 15% showed <1/3 Gd enhancement (reader range=5.2-13.8%). MFS initially showed perilesional oedema (reader range=89.7-93.1%) in many cases, but the presentation of oedema was inconsistent [reader range: i) diffuse oedema (50.0-67.3%), and ii) circumscribed oedema (32.7-50.0%)]. As a relatively characteristic sign of MFS, the tail sign was found in less than 50% of the examined group (reader range=41.4-44.8%). Table II shows the parameters of the analysed MFS separately by each radiologist (reader).

The Cohen's kappa coefficient results confirm the relatively high interrater variability and difficulties in evaluating the MRI examinations. Assessment of the tumour margin showed only a slight agreement (κ=0.19), while the assessment of appearance (κ=0.27) and presentation of oedema (κ=0.27) showed fair agreement. Perilesional oedema (κ=0.55) and tail sign (κ=0.60) were diagnosed with a moderate agreement, and the extent of Gd enhancement (κ=0.65) and the tumour localization (κ=0.74) showed substantial agreement, however, the range of results must be considered as indicated by the 95%CI (Table III).

Discussion

In the current study, our group analysed a single-centre cohort of MFS patients treated and diagnosed at a sarcoma centre. All patients in the cohort underwent standardized preoperative MRI examinations. The unique histopathological characteristics and growth patterns, such as the lack of a pseudocapsule limiting tumour growth and the tendency to spread along the fascial layers, renders MFS a difficult-to-treat lesion among orthopaedic tumour surgeons (16, 17). These characteristics are associated with high recurrence rates (up to 79%) regardless of the tumour grade, depth or size (18, 19).

The cohort in the present study is comparable to those of other studies concerning the age distribution, tumour localization and tumour size (6, 12, 17, 20-24). Defining the tumour localization on preoperative MR images is an important step for surgical planning. Although we were able to detect a slight but insignificant difference in OS based on these MR imaging patterns, the tumour localization could not predict it, as previously shown (25). Nevertheless, the tumour localization is an important aspect when it comes to planning the tumour resection because wide resection of epifascial and epi/subfacial tumours can often be achieved more easily by surgeons with better defined resection margins than deep subfacial MFS with close contact to relevant vascular and nerve structures. We could not identify the contrast enhancement as a prognostic factor of overall survival but subjectively emphasize that this sequence can be valuable for preoperative planning. The histopathological findings often show a spread of the MFS and a resulting positive tumour margin, although detailed preoperative surgery planning based on MR imaging according to the recommendations of Kikuta *et al*. (17), for example, was used. Kaya *et al*. have described positive tumour margins in 41% of their cohort, although they developed a surgical plan

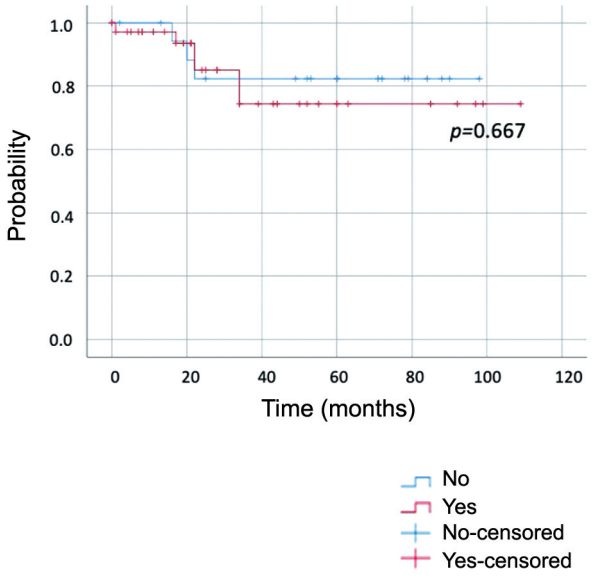

Figure 1. *Kaplan-Meier Curve showing the statistical analysis of survival in months after initial diagnosis and its correlation with the tail-sign (no/yes).*

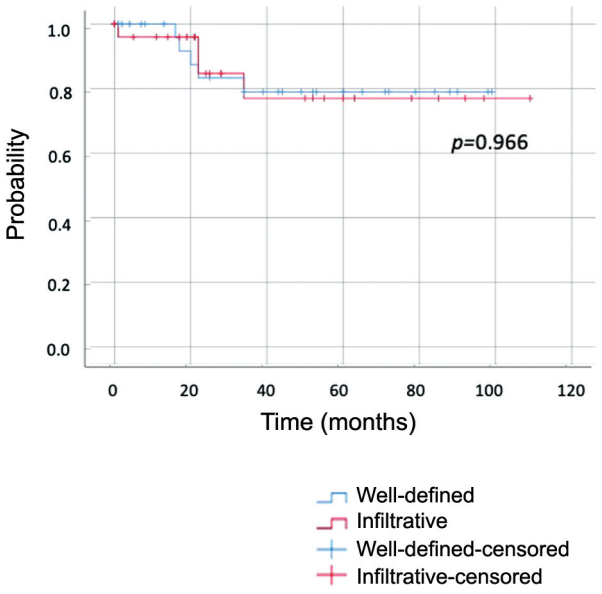

Figure 3. *Kaplan-Meier Curve showing the statistical analysis of survival in months after the initial diagnosis and its correlation with the tumour margins (well-defined/infiltrative).*

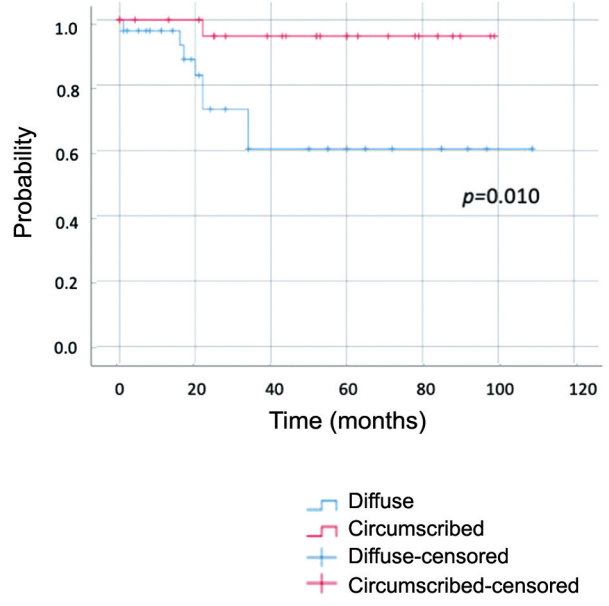

Figure 2. *Kaplan-Meier Curve showing the statistical analysis of survival in months after the initial diagnosis and its correlation with the presentation of perilesional oedema, if present (diffuse/circumscribed).*

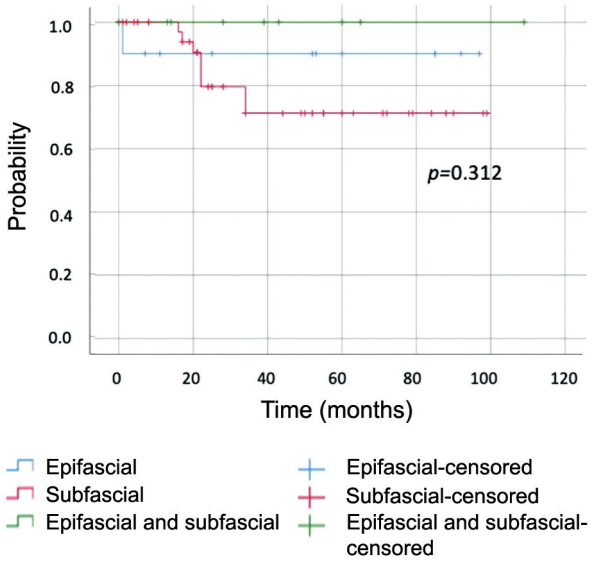

Figure 4. *Kaplan-Meier Curve showing the statistical analysis of survival in months after the initial diagnosis and its correlation with the localization of the tumour (epifascial/subfascial/epifascial and subfascial).*

to remove the tumour with wide surgical margins (26). Manoso *et al*. have confirmed these results in their cohort and emphasized the need for contrast-enhanced MRI during preoperative planning (19).

Independent from tumour localization, histologically-negative tumour margins are an important goal in MFS treatment (27). Positive tumour margins are considered a risk factor for local recurrence in sarcoma surgery (28-31).

Table II. *Frequency of radiological parameters in 58 myxofibrosarcoma (MFS) patients. Readers refer to skeletal radiologists with 25 (A) and 7 years (B) of professional experience. Gd: Gadolimium.*

Radiological parameters	Reader A	Reader B
Localization, n (%)		
Epifascial	10 (17.2)	10 (17.3)
Subfascial	40 (69.0)	34 (58.6)
Epi- and subfascial	8 (13.8)	14 (24.1)
Appearance, n (%)		
Multinodular	23 (39.7)	9 (15.5)
Mass-like round/oval	33 (56.9)	44 (75.9)
Superficial spreading	2 (3.4)	5 (8.6)
Margin, n (%)		
Well-defined	31 (53.5)	32 (55.2)
Infiltrative	27 (46.5)	26 (44.8)
Extent of enhancement Gd in T1, n (%)		
<1/3	3 (5.2)	8 (13.8)
1/3-2/3	23 (39.6)	21 (36.2)
>2/3	32 (55.2)	29 (50.0)
Perilesional oedema, n (%)		
Yes	54 (93.1)	52 (89.7)
No	4 (6.9)	6 (10.3)
Presentation of oedema, n (%)		
Diffuse	27 (50.0)	35 (67.3)
Circumscribed	27 (50.0)	17 (32.7)
Tail sign, n (%)		
Yes	24 (41.4)	26 (44.8)
No	34 (58.6)	32 (55.2)

Table III. *Cohen's Kappa Coefficient of radiological parameters of MFS. Readers refer to skeletal radiologists with 25 (A) and 7 years (B) of professional experience. CI: Confidence interval; Gd: gadolinium.*

Radiological parameters	Cohen's Kappa Coefficient (95%CI) Reader A/B
Localization	0.74 (0.54-0.94)
Appearance	0.27 (0.07-0.48)
Margin	0.19 (0.08-0.46)
Extent of enhancement Gd in T1	0.65 (0.43-0.88)
Perilesional oedema	0.55 (0.30-0.79)
Presentation of oedema	0.27 (0.00-0.54)
Tail sign	0.60 (0.33-0.87)

Kazutaka *et al*. have emphasized the importance of preoperative planning for the surgical treatment of MFS and have shown a significantly higher 5-year survival rate after planned surgical treatment compared to unplanned one in their cohort (3). Kaya *et al*. have described the correlation between MR images and the histological infiltrative growth patterns of MFS, suggesting a correlation between the definition of tumour margins on MR imaging and the overall prognosis (32). In contrast to their results, we could not detect a prognostic value of tumour margins as visualized on MR images (well-defined/ infiltrative) in our cohort when analysing overall survival. We could, however, confirm the results reported by Iwata *et al*., who showed no difference between superficial and deep, or between upper and lower limb localization (33). On one hand, this result is surprising considering the risk of positive tumour margins after resection; on the other hand, all patients in the cohort underwent surgery performed by very experienced tumour surgeons at a specialized centre, where the problem of defining the margins has long been known and considered during the planning phase.

Perilesional oedema is a common MR finding in MFS. To the best of our knowledge, our study is the first to address this fact in detail (circumscribed/diffuse) and the correlation with overall patient survival. Overall patient survival was significantly correlated with the presence of diffuse oedema on MRI, reflected by a hazard ratio of 9.3. Interestingly, the subgroup analysis showed no difference in the number of negative margins and a slight difference in the R1 status. However, given the small number of patients, the histological results showed twice as many Rx resections (7.4% vs. 14.8%) in the group with diffuse oedema on MRI and a higher tendency for metastases (19% vs. 59%). These observations may explain the significantly lower survival in patients with diffuse oedema, although statistical power is lacking in the subgroup analysis. This might explain the results reported by Manoso *et al*., who have described an increased local failure rate of up to 80% in patients with perilesional oedema in their cohort that underwent planned resection compared to those that underwent unplanned resection (19). The authors highlighted an increased T2-weighted signal as a possible prognostic factor (19). We were unable to explain the histopathological reason for this finding, especially since the subgroups do not differ with regard to histological analysis of tumor margins.

The "tail sign" is described as a curvilinear extension of high T1 signal intensity extending from the primary tumour along anatomical structures, such as the fascia, representing the histological infiltrative border in the surrounding tissue (12, 34). This pattern is regarded as a typical sign of MFS on MRI. Several studies have addressed the origin and diagnostic value of the tail sign, such as Lefkowitz *et al*., who documented this pattern in up to 77% of cases in their series. These authors highlighted the high value of the tail sign for the diagnosis of MFS and emphasized the need to alert the surgeon of this pattern so as to include the tail in their resection 12). The detection of the tail sign had no effect on overall survival in our cohort. Yoo *et al*. (6), have, however, reported a significantly worse local recurrence free survival if this sign would be identified on MRI, even though overall survival was not discussed in their study.

Concerning the reproducibility of different features on MR imaging, there were no comparable data on the interrater variability of preoperative MR examinations of MFS; the results can only be compared to other entities. Notably, kappa values cannot be directly compared between different studies addressing different radiological signs and diseases. However, a kappa value of 0.74 is comparable to values reported in some other studies examining radiological variability. Lunkiewicz *et al*. have obtained comparable kappa values for the localization of breast lesions (35) in their cohort. Ochsmann *et al*. have reported a kappa of 0.64 when analysing CT scans concerning the localization of abnormalities in the lung parenchyma (36). Sala *et al*. have identified a comparable interrater agreement (κ=0.75) for prostate tumour localization on MR Imaging (37). Overall, interrater variability in the localization of other malignant entities seems to be similar.

The appearance of the tumour showed only a fair agreement (κ=0.27) among the different observers, indicating the lack of clear definitions and emphasizing the special and uncommon tumour growth patterns of MFS. Mentzel *et al*. have described the growth patterns of focal superficial MFS tumours extending to the deep fascia, losing their clear nodular appearance in the process, and converting to a different and more infiltrative uncharacteristic appearance (5). MFS tumours are very heterogeneous in appearance (38), with variable histological proportions. This finding explains why surgeons are often faced with unexpectedly higher tumour grades after resection than previously indicated by biopsy (39).

The interrater variability concerning tumour margins is important, and we must emphasize this fact as one of the most important problems during preoperative planning. With a kappa value of 0.19, we detected slight agreement concerning the tumour margin on preoperative MRI. Our study confirms the findings of other workgroups that have examined the MRI and histological growth patterns together with the recurrence rate of MFS (14, 19). Kaya *et al*. have stated that abnormal signal intensity of soft tissue may be absent at the periphery of the tumour in some cases of MFS, even if focal tumours show infiltrative extensions (32). Thus, preoperative planning using tumour margins on MRI scans could conceivably lead to incorrect decisions regarding the resection lines, leading to poor results and high recurrence rates.

In our cohort, we demonstrated a moderate (κ=0.55) overall interrater agreement with regards to perilesional oedema, which, as stated above, is important, as diffuse oedema is significantly correlated with overall survival. However, one aspect has to be considered from a statistical point of view. The kappa coefficient in our cohort was relatively low although both readers showed a high concordance regarding certain features in the vast majority of the patients. This seems to be a methodology issue, even though the kappa coefficient serves as an assessment criterion for interrater variability. Thus, if the initial probability of a feature to occur is high, the significance of kappa can be limited. Since the occurrence of a perilesional oedema is a very common feature of MFS (=high probability to occur), even a 90% agreement of both readers might not be sufficient for achieving a "substantial agreement" as per calculated κ-coefficient (κ>0.61) (15). However, we have the opinion that the presence of perilesional oedema could be a useful tool for estimating OS in patients with MFS. Notably, perilesional oedema can increase, such as after neoadjuvant radiation therapy, making it difficult for the radiologist and the surgeon to evaluate the tumour volume as a part of preoperative planning (40).

Kaya *et al*. have demonstrated multidirectional signal spreading along the fascial plane (tail sign) in 80.9% of their cohort and correlated these signals with histological tumour infiltration. These authors found positive tumour margins in 7 of 17 cases despite being aware of these patterns since the preoperative planning (32). This fact indicates the need to investigate the interrater variability of this MRI pattern. We found moderate agreement (κ=0.60) among the raters, confirming the overall agreement of κ=0.62 and κ=0.67 reported by Lefkowitz *et al*. (12) and Yoo *et al*. (6), respectively.

In conclusion, MFS is a difficult-to-treat entity among musculoskeletal tumours. Special attention must be paid to perilesional oedema on MRI, which, in a diffuse distribution, is significantly correlated with poor OS. The interrater variability in interpretation of MR examinations varies from slight to substantial agreement, and the evaluation is difficult even for experienced musculoskeletal radiologists. Preoperative MRI using standardized protocols and interdisciplinary planning of the resection, involving a musculoskeletal radiologist and a tumour surgeon, seem to be a logical approach to optimize this process and achieve negative resection margins and recurrence-free survival.

Conflicts of Interest

The Authors declare that they have no financial or non-financial competing interests.

Authors' Contributions

HM, VL and CK conceived the study and performed the patient recruitment and statistical analyses. AG and KW performed the radiological evaluations. BH supported the statistical analyses in general and the use of special statistical programs. All surgical planning and procedures were performed by CK and RvER. DP, UL, FL, RB and RvER helped write the article. All authors HM, AG, DP, KW, UL, FL, VL, BH, RB, RvER and CK read and approved the final article.

Acknowledgements

This study was supported (without direct financial support) by the Wilhelm-Sander Foundation (Funding Number 2009.905.2), which is a charitable, non-profit foundation, whose purpose is to promote cancer research.

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Received July 6, 2020
Revised July 25, 2020
Accepted July 28, 2020