Prognostic Factors and Outcomes for Patients With Myxofibrosarcoma: A 13-Year Retrospective Evaluation

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Abstract. *Background:* Soft-tissue sarcomas are rare entities that are divided into approximately 50 histological subtypes. Myxofibrosarcoma (MFS) represents approximately 20% of all soft-tissue sarcomas, especially in elderly patients in their sixth to eighth decades of life. The treatment for soft-tissue sarcomas varies from primary surgical resection to neoadjuvant or adjuvant radiotherapy or cytotoxic chemotherapy. The aim of this study was to evaluate the prognostic factors affecting survival of patients with MFS, taking into account gender, tumour grade, state of the resection margin, local recurrence, use of radiotherapy, presence of metastases and blood levels of haemoglobin and C-reactive protein in a retrospective, single-centre analysis with a minimum follow-up period of 60 months (range=60-156 months). *Patients and Methods:* The study included 34 patients (male/female=20/14). Tumour localization, tumour grade, tumour margins, local recurrence, the use of radiotherapy, the presence of metastasis, and the blood levels of haemoglobin and C-reactive protein preoperatively and during follow-up were evaluated. *Results:* MFS constituted the most common high-grade sarcoma (G2/G3, 79.4%) in our cohort and was generally located in a lower limb (73.6%). Negative margins (R0) were detected in 67.6% of patients after surgical resection, and local recurrence occurred in 23.5% of all patients after a mean disease-free period of 19.4 months. Both parameters exerted no significant influence on survival. Radiotherapy was performed in a neoadjuvant or an adjuvant setting in 50% of patients (eight neoadjuvant, nine adjuvant). Metastasis occurred after a mean of 20.4 months in 38.2% of the patients. Higher C-reactive protein levels showed a trend towards being associated with

worse survival, but the association was not significant ($p=0.084$); haemoglobin level had no influence on the survival rate ($p=0.426$). Tumour grade and metastasis were significant prognostic factors of survival (log-rank test $p=0.041$ and $p=0.00007$). Ten patients (29.4%) died due to MFS during our follow-up period. *Conclusion:* The tumour grade and metastasis of MFS are independently associated with disease-specific survival, whereas negative surgical margins, local recurrence and blood levels of C-reactive protein and haemoglobin were not significant prognostic factors. The understanding of the molecular biological patterns that result in the metastasis of these tumours will help develop better treatment plans in the future.

Soft-tissue sarcoma is a rare disease with an annual incidence of approximately 2-5 per 100,000 per year (1). Divided into approximately 50 histological subtypes, it represents a very heterogenic group of tumour entities. Therefore, the treatment for soft-tissue sarcoma varies from primary surgical resection to neoadjuvant/adjuvant cytotoxic chemotherapy. Notwithstanding the availability of treatment, nearly 5,000 patients die as a consequence of this disease in the U.S. each year, with approximately 12,000 new diagnoses made annually (2). Among the wide variety of soft-tissue sarcomas, one of the most common found in elderly people is myxofibrosarcoma (MFS), representing approximately 20% of all soft-tissue sarcomas (3). First described in the 1970s by Angervall *et al.* and specified as an independent disease by the World Health Organization (WHO) in 2002, MFS holds a special position as a difficult-to-treat tumour among the 50 subtypes (4) because it shows different growth patterns, resulting in a strong tendency for local recurrence (5).

The gold-standard treatment for MFS is surgical resection with histologically negative margins, which has superior results and good clinical outcomes compared to exclusive radiotherapy/chemotherapy (6, 7). However, negative margins are sometimes difficult to obtain because of the unusual growth patterns along fascial planes with infiltrative activity, which is described as a tail-like growth pattern (5, 8-11). This

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difficulty in obtaining clean margins results in higher recurrence rates than other soft-tissue sarcomas, reaching up to 79% (8, 12). The second problem is the tendency for metastasis to the lungs and lymph nodes (6). Recent studies have examined prognostic factors, aiming to identify patients with a major risk of treatment failure (7). Previous studies reported small cohorts with magnetic resonance imaging-diagnostic criteria or histopathological expression of different biomarkers. Our cohort represents a large number of patients with MFS with extensive clinical patient records.

Therefore, the aim of this study was to determine the prognostic factors influencing the survival of patients affected by MFS taking into account the tumour grade, histological subtype, state of resection, size, location, metastases and recurrence in a retrospective, single-centre analysis over the course of 13 years.

Patients and Methods

We retrospectively reviewed our institution's database to identify patients who underwent treatment for the diagnosis of MFS from January 2005 to August 2016. We identified 53 patients (male/female=32/21) with a median age of 65.5 years (range=26-94 years) at the time of diagnosis of MFS (Figure 1). All patients were primarily treated with resection at our Institution. We recorded the age (at the time of diagnosis), gender, localization, grade (G1, G2 and G3), tumour margin status (R0: negative/clear margins, R1: positive/involved margins (microscopic), R2: positive/involved margins (macroscopic), Rx: the presence of residual tumour cannot be assessed), the use of radiation therapy (neoadjuvant, adjuvant), the use of chemotherapy, survival, recurrence, metastases (location, time of occurrence), laboratory values (leucocyte count, C-reactive protein (CRP) level, and haemoglobin level) and duration of follow-up (months from diagnosis). Survivorship analysis was performed using the Kaplan-Meier method. Prognostic factors and their influence on mortality were determined using the log-rank test (Mantel-Cox). All data are reported as the means, standard deviations, and percentages, where applicable. The minimum follow-up period for 53 patients was 24 months (range=24-156 months); for 34 patients (male/female=20/14), the minimum follow-up period was 60 months (range=60-156 months, median=78 months). Statistical analysis was performed using SPSS 22.0 (IBM, Armonk, NY, USA).

Results

Overall, we determined that there were 25 tumours (73.6%) in 18 patients (54.1%) located in the lower limb, especially in the thigh, followed by the upper limb in eight patients (23.6%, Figure 2). The overall survival considering all 53 patients was 81.1% at 24 months after the initial diagnosis, and the overall survival of the 34 patients with a minimum follow-up period of 60 months was 70.6% (Figure 3). In our study, the survival of females was better than that of males, but this difference was not statistically significant (Figure 4; log-rank test $p=0.197$). Concerning the tumour grade in the 34 patients with the longer follow-up period, there were

seven (20.6%) G1 tumours, 14 (41.2%) G2 tumours, and 13 (38.2%) G3 tumours. The tumour grade significantly positively correlated (log-rank test $p=0.041$) with patient survival, with those with G1 tumours having best survival (Figure 5). All patients underwent surgical resection. Negative margins (R0) were detected in 23 out of the 34 patients (67.6%), five (14.7%) were classified as R1, one as R2 (2.9%), and two as Rx (5.9%). Three patients had no available information about the resection margins. Compared to patients with R0 resection margins, patients with R1 resection margins did not have poorer survival (Figure 6). Seventeen patients (50%) underwent radiation (neoadjuvant in eight, adjuvant in nine, Figure 7). All patients who underwent radiation had G2 or G3 tumours (high-grade sarcoma). There were no significant differences in the rates of survival among patients who received neoadjuvant radiotherapy, adjuvant radiotherapy and no radiotherapy (log-rank test $p=0.055$). No patient underwent chemotherapy.

Local recurrence was detected in eight patients (23.5%), but local recurrence had no effect on overall survival ($p=0.757$, Figure 8). The mean time to local recurrence was 19.4 months. We observed metastases in 13 (38.2%) out of the 34 patients. The occurrence of metastasis significantly negatively correlated (log-rank test $p=0.00007$) with patient survival. The mean time to the first appearance of metastasis was 20.5 months. The survival of patients with metastases is illustrated in Figure 9. Serum parameters were analysed preoperatively the day before resection of MFS. A high CRP level demonstrated a tendency to be associated with worse survival, but without statistical significance (log-rank test $p=0.084$, Figure 10). The haemoglobin level was also measured preoperatively and had no association with the survival outcome (log-rank test $p=0.426$, Figure 11). Ten patients (29.4%) died due to MFS during our follow-up period. The survival rate was significantly affected by the tumour grade and presence of metastases (Figures 3, 5 and 9). Patients with metastases had significantly worse overall survival than patients without metastases (hazard ratio=2.97, $p=0.005$) and than patients with G3 MFS (hazard ratio=1.56, $p=0.024$).

Discussion

In the current study, our working group retrospectively analysed a single-centre cohort treated at a national sarcoma centre; members of the cohort had a history of MFS and a median follow-up period of 78 months. We sought to determine the prognostic factors and their influence on mortality, recurrence and metastasis. MFS represents approximately 20% of all sarcomas in adults and is known for unique histopathologic characteristics and growth patterns, such as the lack of a pseudo-capsule limiting tumour growth and the tendency to spreading along fascial layers, making it known as a difficult to treat lesion among

Figure 1. Age of distribution of study collective.

Figure 2. Frequency of tumour localisation.

tumour surgeons (3, 8). The survival rate was highly dependent on the tumour grade, the achievement of negative margins during surgery, and metastasis. Additionally, certain serological markers were found to be prognostic factors.

To the best of our knowledge, this is the most up-to-date report providing a comprehensive epidemiological and prognostic evaluation of MFS in a large population treated at a specialized centre.

Localization and overall survival. In the present study, the age distribution of patients suffering MFS was comparable to that in the existing literature. Our cohort was predominantly male, with a median age of 65.5 years, which is similar to the cohorts of Kikuta *et al.* (8), Look Hong *et al.* (10) and Dewan *et al.* (9). The most common tumour site was the lower extremity, with 60% of the tumours in this study found in the thigh, followed by the lower leg and upper arm, confirming the findings of

Figure 3. Kaplan–Meier curve showing statistical analysis of overall survival in months after initial diagnosis of myxofibrosarcoma. Minimum follow-up of 60 months, 34 patients.

Figure 4. Kaplan–Meier curve showing statistical analysis of survival in months after initial diagnosis according to gender; log-rank $p=0.197$. Minimum follow-up of 60 months, 34 patients.

Daniels *et al.* (11) and Sambri *et al.* (12). We found an overall 5-year survival rate of 70.6%, which was slightly lower than the 80% found by Sanfillipo *et al.* (5). Dewan *et al.* found a 5-year survival rate of 63% but included mostly patients with high-grade (G3) tumours in their cohort (9). In our cohort, the overall survival rates did not significantly correlate with the location of

Figure 5. Kaplan–Meier curve showing statistical analysis of survival in months after initial diagnosis according to grading of myxofibrosarcoma; log-rank $p=0.041$. Minimum follow-up of 60 months, 34 patients.

Figure 7. Kaplan–Meier curve showing statistical analysis of survival in months after initial diagnosis according to radiotherapy of myxofibrosarcoma; log-rank $p=0.055$. Minimum follow-up of 60 months, 34 patients.

Figure 6. Kaplan–Meier curve showing statistical analysis of survival in months after initial diagnosis according to resection margins of myxofibrosarcoma; log-rank $p=0.058$. Minimum follow-up of 60 months, 34 patients.

Figure 8. Kaplan–Meier curve showing statistical analysis of survival in months after initial diagnosis according to local recurrence of myxofibrosarcoma; log-rank $p=0.757$. Minimum follow-up of 60 months, 34 patients.

the MFS or the gender of the patients, although we detected a trend towards a slightly higher survival rate for female than for male patients (see Figure 4). In the literature, the survival rate of female patients seems to be slightly better than that of male

patients, although the underlying reasons remain unclear. We confirmed the results of Abbott *et al.* who found a better survival rate for females with retroperitoneal sarcoma than males in their cohort of 1199 patients (13).

Figure 9. Kaplan–Meier curve showing statistical analysis of survival in months after initial diagnosis according to metastasis of myxofibrosarcoma; log-rank $p=0.00007$. Minimum follow-up of 60 months, 34 patients.

Figure 11. Kaplan–Meier curve showing statistical analysis of survival in months after initial diagnosis according to haemoglobin level before operation; log-rank $p=0.426$, cut-off <13 g/dl for males, <12 g/dl for females. Minimum follow-up of 60 months, 34 patients.

Figure 10. Kaplan–Meier curve showing statistical analysis of survival in months after initial diagnosis according to serum level of C-reactive protein (CRP) before operation; log-rank $p=0.084$, cut-off $=0.5$ mg/dl. Minimum follow-up of 60 months, 34 patients.

Grading. In terms of histopathology, most of the patients in our cohort were specified as having high-grade MFS (34 patients), in addition to 14 with G2 MFS and 13 with G3 MFS. The proportion of patients with G3 tumours was slightly higher than that reported by Sanfilippo *et al.* (5). Nevertheless, the low incidence of G1 tumours confirmed the findings of

Dewan *et al.* (10) and Sanfilippo *et al.* (5). No patients with low-grade G1 MFS died of the disease in our cohort, confirming that grading is an important prognostic factor. Patients who had high-grade G3 MFS had the worst 5-year survival rates among patients with different grade tumours in our study. Compared to the 73.2% survival rate reported by Sambri *et al.* (12), our survival rate of 46.2% was significantly lower. Our 5-year survival rate was lower than those found by other working groups, with 5-year survival rates ranging from 55 to 63%. Patients with G2 tumours had a significantly better survival rate than those with G3 tumours, which is in agreement with the findings of the existing literature.

Negative margins and local recurrence. Negative margins and local recurrence are important considerations in the treatment of MFS. Kikuta *et al.* described the unique histological growth patterns of MFS in their cohort of 30 patients with recurrence of MFS. Histologically negative margins were achieved in only 40% of their cohort (8). This working group clearly showed the relationship between positive margins after the first surgery and the incidence of local recurrence. The unique growth patterns of MFS are most likely responsible for this. These special growth patterns are even visible on the preoperative MRI and are known as tail signs, representing fascial enhancement extending from the tumour margin (14). In our series, we achieved negative margins in 67.6% (23 patients), with positive margins in six patients. These proportions are

slightly lower than those in the cohort of Kikuta *et al.* (8). However, the cohorts are not directly equivalent, as Kikuta *et al.* included amputees in their negative margins subgroup. We excluded patients who underwent amputation because limb salvage was one of our primary treatment goals. We confirmed the results of the large series by Mutter *et al.*, who also excluded patients who underwent amputation from their cohort (15). Nevertheless, we must highlight the issue of the definition of negative margins because it is not standardized. Common definitions of negative margins range between 1 mm and 5 cm; some patients may be classified as having negative margins by one author and as having positive margins by another (5, 8). The recent work of Harati *et al.* showed that a tumour-free margin >1 mm is clinically relevant (20), which could help define a standard to be applied in a meta-analysis of a large number of cohorts in the future. We analysed resection margins by gross and microscopic examinations and then defined a clear tumour-free margin of at least 1 mm from the edge of the inked specimen. As described in recent studies, a negative margin can be defined as >1 mm in MFS and in other soft-tissue sarcoma (16-18). We calculated a 5-year survival rate of 78.3% for patients with negative margins. Surprisingly, the 5-year survival rate for patients with R1 positive margins was slightly but not significantly higher than that of patients with negative margins. This finding could be the result of statistical bias, as only one out of the 13 patients with positive margins (R1) died during the follow-up period. We have no other explanation. The worst survival rate was found for patients with Rx positive margins; these findings reflect observations in previous studies and are comparable with observations in studies of other soft-tissue sarcomas (19).

In our cohort, 10 patients developed local recurrence in the follow-up period. All of these patients had G2 (3) or G3 (7) tumours. Local recurrence occurred independently of the state of the margins; in fact, most patients with local recurrence had histologically negative margins. We detected a worse 5-year survival rate in the group with local recurrence than in that without local recurrence, although the difference between these groups was not significant. Thirteen patients also developed distant metastases. Local recurrence is a major problem for surgeons and patients. Reoperation is much more difficult due to neurovascular structures and scar tissue because most MFSs are located deep in the thigh. This fact was examined by Kikuta *et al.* in their cohort of patients with local recurrence, who had a 5-year second recurrence-free survival rate of 9.8% (8).

Distant metastases. Thirteen patients (38.2%) developed distant metastases during the study period. The average time to appearance of distant metastases was 20.5 months. The detected metastases were located mainly in the lung (n=12) and the lymph nodes (n=2). We detected one in the gluteal muscles, one in the periossar and one in a vertebra. The rate

of development of metastases varies in the literature from 9.5-27.5% (5, 6, 9, 10, 15, 20, 21). In our cohort, the rate of metastasis was equivalent to the highest reported in the literature; therefore, we confirmed the findings of Tsuchie *et al.*, who also reported a comparable rate of metastases (6). All other authors reported rates of metastasis between 9.3 and 23%. We have no explanation for these findings; we can only surmise that our tumour cohort had different mitotic activity, which is a known risk factor for distant metastases, and different tumour-specific characteristics, such as the presence of necrosis (5, 22, 23). The tumour sites in our cohort match those in recent reports in the literature. However, from a prognostic point of view, we found a clear correlation between metastasis and poorer survival. Patients who developed distant metastases after surgery had a 5-year survival rate of 30.8% while those who did not had a 5-year survival rate of 95.2%.

Serum analysis. Recent studies have addressed the effect of systemic inflammation on disease progression and metastases in patients with cancer. Only a few studies have addressed this problem in those with soft-tissue sarcomas (24, 25). An elevated preoperative CRP level was discussed as an independent risk factor for poor survival (26). Panotopoulos *et al.* confirmed this in their cohort of patients with liposarcoma and postulated that the level of CRP is a predictor of disease-specific survival in patients with liposarcoma (27). Moreover, preoperative anaemia is known to be associated with shorter 5-year survival rates in patients with cancer, according to the European Cancer Anaemia Survey (28). Nakamura *et al.* noted that anaemia was correlated with poor survival rates in patients with soft-tissue sarcomas (29). To the best of our knowledge, our working group is the first to determine the correlation between the serum level of CRP and survival rates in a cohort of patients with MFS. We did not find any significant correlation between decreased values of haemoglobin and poor survival. A low haemoglobin level is a positive indicator for anaemia; therefore, we confirmed the results of Nakamura *et al.* (32). They reported a 5-year survival rate of 52.6% for patients with anaemia and 79.7% for those without anaemia. We found similar percentages of 60.0% and 77.3%, respectively. Furthermore, we demonstrated an apparent but nonsignificant association between elevated CRP serum level and poor survival ($p=0.084$). This suggests that we can confirm the findings of Szkandera *et al.* (26), who demonstrated a worse survival rate in patients with elevated serum CRP level than in those with a normal level. We calculated nearly the same 5-year survival rate as Szkandera (73.4%) for patients with elevated serum level of CRP (26). The cohort in the study by Szkandera *et al.* included 304 patients with all types of soft-tissue sarcomas (26). The lack of a significant

correlation between the serum level of CRP and survival is probably the result of statistical bias due to the limited number of patients included in our study.

Our study has certain limitations. The small number of patients included in the study limits the statistical analysis, and MFS remains a rare disease; therefore, a multicentre study is needed to solve this problem. We included patients from 2005 onwards and did not have full records regarding interesting new molecular serum markers such as procalcitonin and interleukin. Further studies should address these biomarkers to provide more accurate prediction of tumour prognosis after surgery using serum analysis. Finally, our cohort underwent surgery conducted by four different surgeons, which introduces bias regarding their training levels and experience with MFS.

Conclusion

In conclusion, MFS is challenging for tumour surgeons and oncologists due to its clinical course. Distant metastasis of MFS leads to a poor prognosis. Negative margins after the first surgery are an important finding that can guide the treatment process, emphasizing the need for primary treatment at a referral hospital. New approaches using serum analysis of different biomarkers may be able to guide more precise prediction of survival in the future. However, understanding the molecular biological patterns that result in growth, recurrence and metastasis of these tumour entities will help develop better treatment plans in the future.

Authors' Contributions

HM, VL and CK performed patient recruitment and clinical investigation. UL, AO, AG, RB and RvER conceived of the study, participated in its design and coordination and helped draft the article. All Authors read and approved the final article.

Conflicts of Interest

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

IRB Approval

The Institutional Review Board (IRB) at the Klinikum rechts der Isar approved the study (Faculty of Medicine, Technical University Munich, 441/16).

Each Author certifies that all investigations were conducted in conformity with ethical principles. Written informed consent was obtained from all patients included in the study.

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Consent for Publication

No individual person's data are published in the present work.

Availability of Data and Materials

The datasets supporting the conclusions of this article are included within the article. The raw data can be requested from the corresponding Author.

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