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International Multicenter Retrospective Study From the Ultra-rare Sarcoma Working Group on Low-grade Fibromyxoid Sarcoma, Sclerosing Epithelioid Fibrosarcoma, and Hybrid Forms

Outcome of Primary Localized Disease

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Abstract: The aim of the study was to report the outcome of primary localized low-grade fibromyxoid sarcoma (LGFMS), sclerosing epithelioid fibrosarcoma (SEF), and hybrid LGFMS/SEF (H-LGFMS/SEF). Patients with primary localized LGFMS, SEF, or H-LGFMS/SEF, surgically treated with curative intent from January 2000 to September 2022, were enrolled from 14 countries and 27 institutions. Pathologic inclusion criteria were predefined by expert pathologists. The primary endpoint was overall survival (OS). Secondary endpoints were crude cumulative incidence (CCI) of local recurrence (LR), CCI of distant metastases (DM), and post-metastases OS (p-OS). Two hundred ninety-four patients (239 LGFMS, 32 SEF, and 23 H-LGFMS/SEF) were identified. At a median(m-) follow-up (FU) of 57.1 months, 12/294 patients died. The 5- and 10-year OS were 99.0% and 95.9% in LGFMS, 86.2% and 67.0% in SEF, and 84.8% and 84.8% in H-LGFMS/SEF, respectively. Predictors of worse OS included pathology, age at surgery, systemic therapy, and radiotherapy. LR developed in 13/294 (4.4%) patients. The observed m-time to LR was 10.7 months. The 5- and 10-yr CCI-LR were 4.7% in LGFMS and 6.6% in SEF, respectively. There were no LR events in H-LGFMS/SEF. The sole predictor of higher risk of LR was histology. DM developed in 23/294 (7.8%) patients. The observed m-time to DM was 28.2 months. The 5- and 10-yr CCI-DM were 1.3% and 2.7% in LGMFS, 29.9% and 57.7% in SEF, 48.9% and 48.9% in H-LGFMS/SEF, respectively. Predictors of higher risk of DM were histology, systemic therapy, and radiotherapy. Primary localized LGFMS treated with complete surgical resection has an excellent prognosis, while about 50% of H-LGFMS/SEF and SEF develop DM within 5 to 10 years. Very long-term FU is needed to understand absolute cure rates.

Key Words: low-grade fibromyxoid sarcoma, sclerosing epithelioid fibrosarcoma, hybrid forms, localized disease, prognostic factors, survival

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Low-grade fibromyxoid sarcoma (LGFMS) and sclerosing epithelioid fibrosarcoma (SEF) are ultra-rare sarcomas.[1] They share morphologic, immunohistochemical, and molecular features but are considered distinct though related entities by the current WHO classification, and cases with hybrid morphology are recognized (H-LGFMS/SEF).[2] LGFMS and hybrid forms are characterized in the majority of cases by *FUS::CREB3L2* fusions,[3,4] whereas the most common molecular alteration in pure SEF is an *EWSR1::CREB3L1* gene fusion.[5] Immunohistochemically, almost all cases of LGFMS and ~70% of SEF show strong diffuse cytoplasmic expression of MUC4.[6,7]

LGFMS mainly occurs in the deep soft tissue of the extremities of young adults and shows indolent behavior, while SEF primarily affects middle-aged and elderly patients and is more aggressive.[8,9] Surgery is considered the standard treatment for localized disease in both subtypes, while radiotherapy is commonly administered when wide excision is not feasible.[10] There are a few small series on the molecular profiling of H-LGFMS/SEF,[11] but there are no data regarding treatments and outcomes in this specific subtype.

In this global retrospective study within the *Ultra-Rare Sarcoma Working Group* (*URSWG*), we aimed to understand the natural history and the prognostic factors of patients with primary localized LGFMS, SEF, or H-LGFMS/SEF.

METHODS

This is an international retrospective multicenter study conducted within the URSWG. All consecutive patients of any age with primary localized LGFMS, SEF, and H-LGFMS/SEF surgically treated with curative intent at the participating institutions between January 2000 and September 2022 were retrospectively identified.

Data retrospectively retrieved included patient gender, age at diagnosis, site of origin, histologic type, neoadjuvant/adjuvant treatments, type of surgery, and margin status.

Eligible patients had a pathologically confirmed diagnosis of LGFMS, SEF, or H-LGFMS/SEF (requiring strong MUC4 immunohistochemical expression and/or 1 of the following: *FUS*/*EWSR1* rearrangement*; EWSR1*/*FUS::CREB3L1*/*CREB3L2*/*CREM* fusions), as predefined and agreed by a panel of sarcoma expert pathologists within the *URSWG*. The inclusion criteria are detailed in Supplementary Data-Synopsis.

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The indication for radiotherapy (RT) differed among institutions and was generally recommended when a higher risk of relapse was estimated on clinical grounds.

Systemic therapy was rarely administered at the discretion of each expert sarcoma team among institutions.

Statistical Analysis

Patients, disease, and treatment characteristics were summarized using standard descriptive statistics.

The primary endpoint was overall survival (OS). Secondary endpoints were crude cumulative incidence (CCI) of local recurrence (LR), CCI of distant metastases (DM), and post-metastases OS (p-OS). Cox models were fitted to analyze the association between OS and the putative prognostic covariates; Fine and Gray models were used to analyze LR and DM incidence.

OS was defined as the time from diagnosis until death due to any cause. CCI-LR and CCI-DM were estimated in a competing risk setting, that is, considering the first local recurrence/distant metastases as occurring events and including deaths without events among the competing events. p-OS was defined as the time from DM until death due to any cause. Patients alive and without the event of interest were censored at the last known follow-up. The OS and p-OS curves were estimated with the Kaplan-Meier method, and compared with the log-rank test. The CCI curves of LR and DM were compared using the Gray test.

RESULTS

Patient and Tumor Characteristics

Overall, 294 patients with primary and localized LGFMS (239 patients), SEF (32 patients), and H-LGFMS/SEF (23 patients) were surgically treated with curative intent at the participating institutions from January 2000 to September 2022 and were considered for the present study. We excluded 3 patients with primary localized disease (3/297 patients) who did not receive surgery for primary treatment.

Baseline patient, histopathological/molecular, and treatment characteristics are shown in Table 1. Examples of morphologic and immunohistochemical features of the 3 histologic subtypes are shown in Figures 1 and 2.

Molecular analysis was conducted in 160/239 (67%) LGFMS patients, detecting a positive *FUS/EWSR1* rearrangement in 154 cases, including 50% *FUS::CREB3L2*, 4% *FUS::CREB3L1*, 1% *EWSR1::CREB3L1*, and 45% *FUS/EWSR1* rearrangements with no fusion partner specified.

For SEF, molecular analysis was performed in 19/32 (59%) patients, with *EWSR1* rearrangement detected in 15 cases. This included 65% *EWSR1::CREB3L1*, 12% *EWSR1::CREB3L2*, and 23% *EWSR1* rearrangements with no fusion partner specified.

Similarly, in H-LGFMS/SEF, analysis was conducted in 17/23 patients (74%), revealing a positive *FUS/EWSR1* rearrangement in 13 cases. Among these, 31% were *EWSR1::CREB3L1*, 23% were *FUS::CREB3L2*, and 46% were *FUS/EWSR1* rearrangements with no fusion partner specified.

Thirteen out of 294 (4%) patients (4/239 LGFMS, 8/32 SEF, and 1/23 H-LGFMS/SEF) underwent systemic therapy, with the majority (10/13) receiving doxorubicin-based treatment. Among patients who received neoadjuvant systemic treatments and were evaluable for response (3/8 SEF, 1/4 LGFMS, and 0/1 H-LGFMS/SEF), 3 SEF patients were treated with doxorubicin-ifosfamide and had stable disease and 1 LGFMS patient was treated with oral cyclophosphamide and had stable disease. No radiologic responses were observed.

Eighty-seven out of 294 (30%) patients (62/239 LGFMS, 16/32 SEF, and 9/23 H-LGFMS/SEF) received radiotherapy, administered in postoperative setting in 29/87 cases (19/29 after R0 surgery, 5/29 after R1 surgery, 2/29 after R2 surgery, and 3/29 unknown margins).

Median(m-) follow-up (FU) was 57.1 months (interquartile range [IQR]: 20.7, 87.0) overall, 55.7 months (IQR: 19.5, 87.0) in LGFMS, 57.7 months (IQR: 37.1, 90.5) in SEF, and 58.5 months (IQR: 15.9, 81.6) in H-LGFMS/SEF.

Overall Survival

Overall, m-OS was not reached (IQR: 191.4-not reached, Fig. 3). The corresponding 5- and 10-year OS estimates were 96.5% (95% CI: 93.9-99.2) and 92.0% (CI: 87.0-97.2), respectively. m-OS, and 5- and 10-year estimates of OS according to pathology are shown in Table 2. LGFMS was associated with better OS (96.1% 10-year OS) compared with SEF (67.0%) and H-LGFMS/SEF (84.8%). In the overall cohort, older age at surgery (*P* value 0.0050), histologic subtype (*P* value 0.0022), administration of radiotherapy (*P* value 0.0292), and systemic therapy (*P* value 0.0091) were associated with OS in univariable analysis (Supplementary Table 1A, Supplemental Digital Content 1, http://links.lww.com/PAS/B960), while only age at surgery (*P* value 0.0027) was significantly associated with OS in multivariable analysis (Supplementary Table S1B, Supplemental Digital Content 1, http://links.lww.com/PAS/B960).

Local Recurrence

Overall, 13/294 (4.4%) patients experienced LR (10/13 LGFMS, 3/10 SEF, and 0/10 H-LGFMS/SEF). The observed median time to LR was 10.7 months (IQR: 1.8-26.1). The corresponding 5- and 10-year CCI-LR were 5.1% (CI: 2.9-9.0).

The number of events, median time to LR, and 5- and 10-year estimates of CCI-LR according to histologic subtype are shown in Table 2. CCI-LR curves of LR are shown in Fig. 4.

In the overall cohort, SEF histologic subtype (*P* value < 0.0001) was significantly associated with CCI-LR in both univariate and multivariate analysis (Supplementary Table 2A, B, Supplemental Digital Content 2, http://links.lww.com/PAS/B961), while the administration of systemic therapy was the only variable significantly associated with CCI-LR on multivariate analysis (*P* value

TABLE 1. Patient Characteristics

Histologic subtype	LGFMS	SEF	H-LGFMS/SEF
Number of pts with primary disease (%)	239/294 (81.3)	32/294 (10.9)	23/294 (7.8)
Age at surgery (y), median (IQR)	38.0 (27.5-52.0)	47.0 (31.8-55.0)	45.0 (30.0-58.0)
Male/female (%)	119 (49.8)/120 (50.2)	23 (71.9)/9 (28.1)	11 (47.8)/12 (52.2)
Histopathologic/molecular features			
MUC4 expression (%)			
Positive	170 (71.1)	24 (75.0)	19 (82.6)
Negative	3 (1.3)	0 (0.0)	0 (0.0)
Unknown	66 (27.6)	8 (25.0)	4 (17.4)
Number of pts analyzed for *FUS* rearrangement (%)	158/239 (66.1)	2/32 (6.3)	16/23 (73.9)
Positive	152/239 (63.6)	2/32 (6.3)	8/23 (34.8)
FUS::CREB3L2	77/152 (50.7)	1/2 (50.0)	3/9 (33.3)
FUS::CREB3L1	6/152 (3.9)	0/2 (0.0)	0/9 (0.0)
No fusion partner specified	69/152 (45.4)	1/2 (50.0)	5/9 (55.6)
Negative	6/239 (2.5)	0/32 (0.0)	8/23 (34.8)
Number of pts analyzed for *EWSR1* rearrangement (%)	2/239 (0.8)	17/32 (53.1)	9/23 (39.1)
Positive	2/239 (0.8)	15/32 (46.8)	5/23 (21.7)
EWSR1::CREB3L1	2/2 (100.0)	11/15 (73.3)	4/5 (80.0)
EWSR1-CREB3L2	0/2 (0.0)	2/15 (13.3)	0/5 (0.0)
No fusion partner specified	0/2 (0.0)	2/15 (13.3)	1/5 (20.0)
Negative	0/239 (0.0)	2/32 (6.3)	4/23 (17.4)
Primary site (%)			
Extremities	153 (64.0)	14 (43.8)	11 (47.8)
Abdomen / retroperitoneum	21 (8.8)	4 (12.5)	5 (21.7)
Trunk	33 (13.8)	4 (12.5)	3 (13.0)
Other	32 (13.4)	10 (31.3)	4 (17.4)
Treatments of primary disease			
Surgery (%)			
No	0 (0.0)	0 (0.0)	0 (0.0)
Yes	239 (100.0)	32 (100.0)	23 (100.0)
R0	195 (81.6)	28 (87.5)	19 (82.6)
R1	28 (11.7)	1 (3.1)	2 (8,7)
Missing	13 (5.4)	1 (3.1)	1 (4.3)
R2	3 (1.3)	2 (6.3)	1 (4.3)
Radiotherapy (%)			
No	171 (74.1)	16 (50.0)	14 (60.9)
Yes	62 (25.9)	16 (50.0)	9 (39.1)
Systemic therapies (%)			
No	235 (98.3)	24 (75.0)	22 (95.7)
Yes	4 (1.7)	8 (25.0)	1 (4.3)
Status at last follow-up (%)			
Alive, No evidence of disease	211 (88.3)	19 (59.4)	17 (73.9)
Alive, With evidence of disease	5 (2.1)	7 (21.9)	2 (8.7)
Dead	4 (1.7)	6 (18.8)	2 (8.7)
Lost to follow-up	19 (7.9)	0 (0.0)	2 (8.7)

pts indicates patients.

<0.0001) (Supplementary Table 2B, Supplemental Digital Content 2, http://links.lww.com/PAS/B961).

Distant Metastases

Overall, 23/294 (7.8%) patients experienced DM (3/239 LGFMS, 12/32 SEF, and 8/23 H-LGFMS/SEF). The observed median time to DM was 28.2 months (IQR: 16.2-48.8). The corresponding 5- and 10-year CCI-DM were 8.6% (CI: 5.5-13.4) and 14.0% (CI: 8.2-22.6), respectively.

The number of events, median time to DM, and 5- and 10-year estimates of CCI-DM according to histologic subtype are shown in Table 2. CCI-DM curves of DM are shown in Figure 4.

In the H-LGFMS/SEF group, 3/8 *FUS*-positive and 3/4 *EWSR1*-positive patients developed DM; the corresponding 3-year CCI-DM was 37.5% (CI: 10.5-100) and 66.7% (CI: 22.3-100), respectively.

In the overall cohort, SEF and H-LGFMS/SEF histology (P value <0.0001) was significantly related to CCI-DM in both univariate and multivariate analysis, while the administration of radiotherapy and systemic therapy (P value <0.0001) were significantly related to CCI-DM only on univariate analysis (Supplementary Table 3A, Supplemental Digital Content 3, http://links.lww.com/PAS/B962), but not in multivariable analysis (Supplementary Table 3B, Supplemental Digital Content 3, http://links.lww.com/PAS/B962).

Three of 239 patients with LGFMS developed DM: 1 had DM 7.8 months postsurgery for the primary disease, subsequently receiving systemic therapies (pazopanib, liposomal doxorubicin, and pembrolizumab), and was

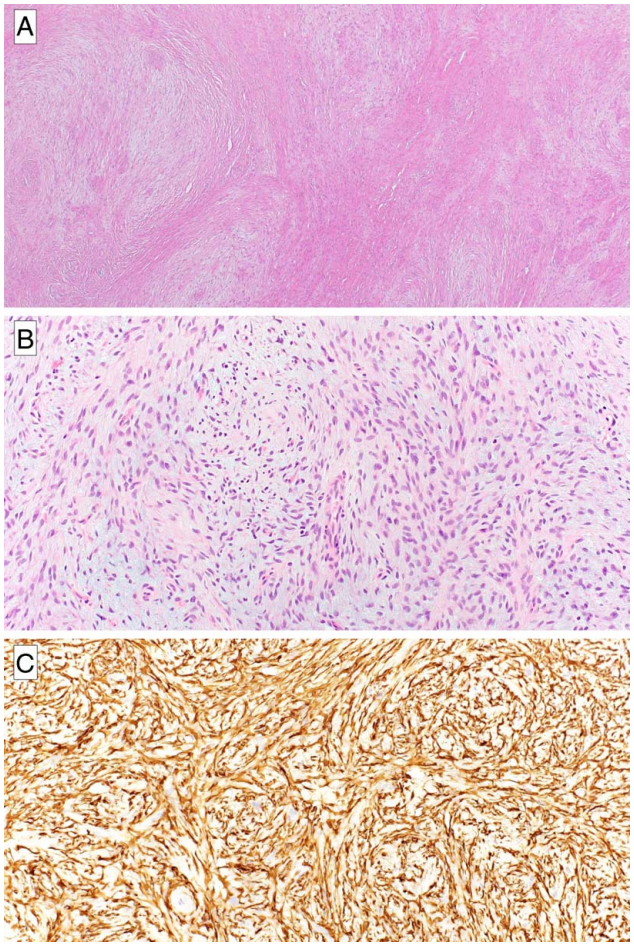

FIGURE 1. Low-grade fibromyxoid sarcoma: morphology and immunohistochemical features. At low power, the typical alternating multinodular myxoid and collagenous stroma can be appreciated (A). The tumor is characterized by bland spindle cells organized in short fascicles set in a fibromyxoid background (B). Strong and diffuse immunopositivity for MUC4 is observed in almost all cases (C).

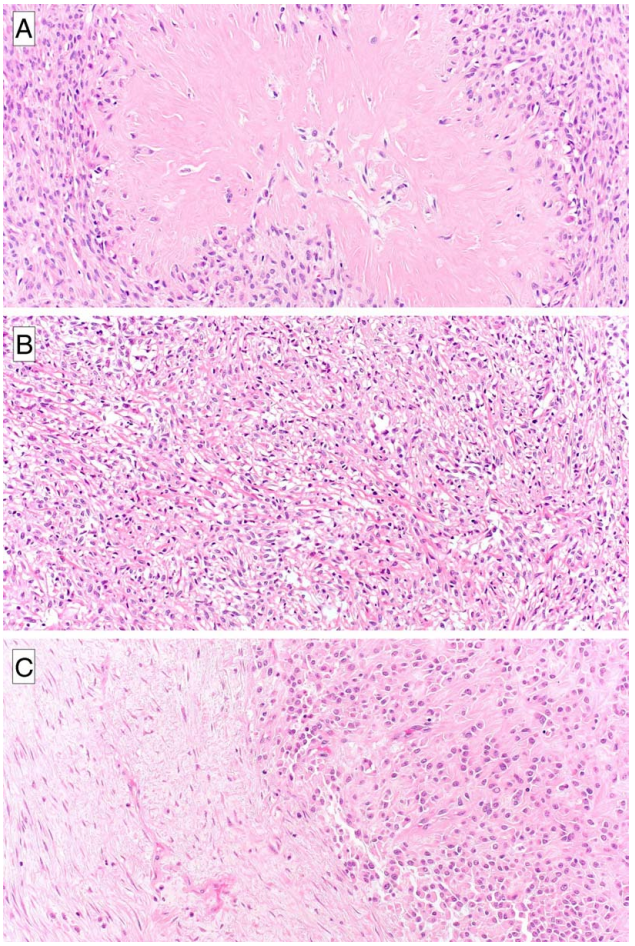

FIGURE 2. Morphologic features of low-grade fibromyxoid sarcoma, sclerosing epithelioid fibrosarcoma, and hybrid forms. An example of LGFMS showing distinctive large collagenous pseudorosettes composed of a central hyalinized collagenous area surrounded by a collarette of neoplastic cells (A). SEF is composed of epithelioid cells organized in cords and nests set in a collagenous stroma (B). The hybrid form is composed of a combination of SEF and LGFMS areas (C).

alive with disease (AWD) at the latest follow-up. Another patient developed DM 47.5 months after primary surgery, underwent twice a complete metastasectomy, and was AWD at the latest follow-up. The third patient developed DM 78.7 months post-primary surgery, underwent complete metastasectomy, and was alive without disease at the latest follow-up.

Post-metastases Overall Survival

Median-p-OS and 5-year estimates of p-OS according to histologic subtype are shown in Table 2. Kaplan-Meyer curves are shown in Figure 5.

DISCUSSION

In this international, multicentric retrospective series, we report data on the largest cohort to date of patients affected by primary, localized, resectable LGFMS, SEF, and H-LGFMS/SEF observed and treated at several sarcoma referral centers over a >20-year time span. We found that localized LGFMS is associated with an excellent prognosis, while about 50% of H-LGFMS/SEF and SEF develop DM within 5 years and 10 years. This suggests that the biology and clinical behavior of H-LGFMS/SEF more closely mimics SEF than LGFMS. No significant prognostic factors other than age and histologic subtype were identified for any of the endpoints analyzed.

This was a retrospective study with inherent limitations. The relatively short m-FU (57 mo) did not allow for a comprehensive analysis of the natural history of the disease, particularly of LGFMS, which may also metastasize many years after diagnosis (observed median time to DM = 47.5 mo), with events occurring many months after the m-FU of the study (1 of the 3 patients who developed DM did so 78.7 mo after surgery). Because of the restricted number of events, our ability to effectively study

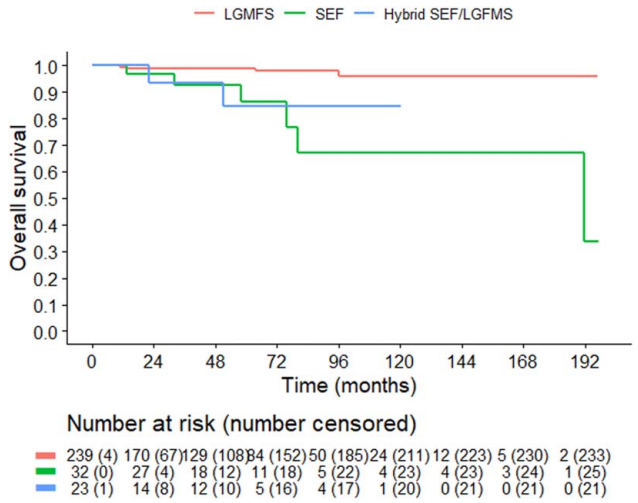

FIGURE 3. Overall survival according to histologic subtype. LGFMS indicates low-grade fibromyxoid sarcoma; SEF, sclerosing epithelioid fibrosarcoma.

the correlation between putative prognostic factors and survival in all histologies is limited. Moreover, among the 27 institutions that took part in the study, the approach to disease was heterogeneous. Consequently, we were not able to thoroughly analyze either the optimal systemic therapy or radiation schedule.

However, to the best of our knowledge, this is one of the largest series of this ultra-rare sarcoma type. We tried to homogenize the population by selecting cases with pathologically confirmed diagnoses based on predefined criteria and only treated by an expert sarcoma team (Supplementary Data-Synopsis).

The chance of cure for localized LGFMS is high with surgery alone with OS close to 100% at 10 years. Patients are usually young (median age 48 y). Hence, as also suggested by the French study,[8] they should be followed for at least 10 years after surgery to monitor for disease recurrence in this young population, as metastases were also seen well above the m-FU. In a 33 LGFMS series from the U.T.M.D. Anderson Cancer Center, 21/33 patients recurred after intervals of up to 15 years.[12]

Conversely, the chance of cure for localized H-LGFMS/SEF and SEF does not exceed 50%. These tumors are more aggressive, tend to recur earlier, and do not seem to significantly benefit from currently available therapies. Indeed, the activity of conventional systemic treatments is very limited,[8,9,13] as we reported in patients with metastatic H-LGFMS/SEF (paper under submission), and also in this study, we did not see any responses to chemotherapy in the neoadjuvant setting (anthracycline-based regimens and oral cyclophosphamide). Therefore, current systemic therapy does not have a clearly defined role for localized LGFMS, SEF, and H-LGFMS.

The LR risk is limited in all histologies. Surgery may be sufficient to control the primary disease. In terms of anatomic locations, there is a nonsignificant trend in favor of better local control in extremities compared with chest and retroperitoneum/abdomen and other sites (Supplementary Table 2, Supplemental Digital Content 2, http://links.lww.com/PAS/B961). This trend is consistent with what is observed in all other sarcoma types and is related to the different anatomic constraints of extremities versus trunk and the ability to perform a wide resection.

RT was administered in around 30% to 40% of cases in the 3 histologies and was not significantly associated with survival benefit or reduction of relapse risk in this cohort. Therefore, the administration of RT may not be needed in all cases, regardless of size, location, or histologic type. As mentioned, all our patients were treated in sarcoma referral centers by a team of expert surgeons who performed a macroscopic complete resection in 90% to 95% of cases. This may well be one of the reasons why the administration of adjuvant radiotherapy was limited and did not influence the LR risk.

TABLE 2. Outcome According to Histologic Subtype

	LGFMS (239 pts)	SEF (32 pts)	H-LGFMS/SEF (23 pts)
Median follow-up, mo (IQR)	55.7 (19.5-87.0)	57.7 (37.1-90.5	58.5 (15.9-81.6)
OS			
m-OS (months)	NR	191.4 (CI: 80.1-NR)	NR
5-yr OS	99.0% (CI: 97.6-100.0)	86.2% (CI: 72.1-100.0)	84.8% (CI: 67.4-100.0)
10-yr OS	96.1% (CI: 91.9-100.0)	67.0% (CI: 45.3-99.2)	84.8% (CI: 67.4-100.0)
LR			
Number of events	10	3	0
Median time to LR (mo)	5.4 (IQR: 1.3-33.5)	24 (IQR: 17-24)	—
5-yr CCI	4.7% (CI: 2.4-9.0)	6.6% (CI: 3.6-31.8)	—
10-yr CCI	4.7% (CI: 2.4-9.0)	6.6% (CI: 3.6-31.8)	—
DM			
Number of events	3	12	8
Median time to DM (mo)	47.5 (IQR: 27.6-63.1)	32.0 (IQR: 25-97)	20 (IQR: 14.7-28.6)
5-yr CCI	1.3% (CI: 0.3-5.2	29.9% (CI: 16.4-54.5)	48.9% (CI: 28.5-83.9)
10-yr CCI	2.7% (CI: 0.8-9.3)	57.7% (CI:30.5-109.1)	48.9% (CI: 28.5-83.9)
p-OS			
m-p-OS (mo)	NR (CI: NR-NR)	83.2 (CI: 42.1-NR)	34.0 (CI: 34.0-NR)
5-yr OS	100% (CI: 100.0-100.0)	64.6% (CI: 38.1-100.0)	43.8% (CI: 10.7-100.0)

H indicates hybrid; LR, local recurrence; m, median; NR, not reached; pts, patients.

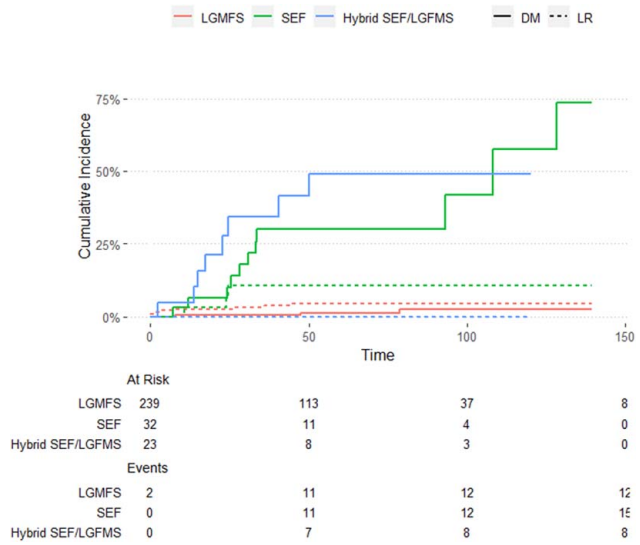

FIGURE 4. Local recurrence and distant metastases according to histologic subtype. SEF indicates sclerosing epithelioid fibrosarcoma; LR, local recurrence; DM, distant metastases.

The main driver of prognosis is the DM risk, which is low in LGFMS and high in H-LGFMS/SEF and SEF. The 5-year OS was 100% in LGFMS, 64.6% in SEF, and 43.8% in H-LGFMS/SEF, and survival does not seem to be strongly correlated with the need for RT or systemic therapy.

We observed that the molecular profile of LGFMS and SEF was consistent with previous reports. Indeed, the most common alteration in LGFMS was *FUS::CREB3L2*, and in SEF was *EWSR1::CREB3L1*, as reported.[3–5,14,15] Molecular analysis of H-LGFMS/SEF revealed different molecular

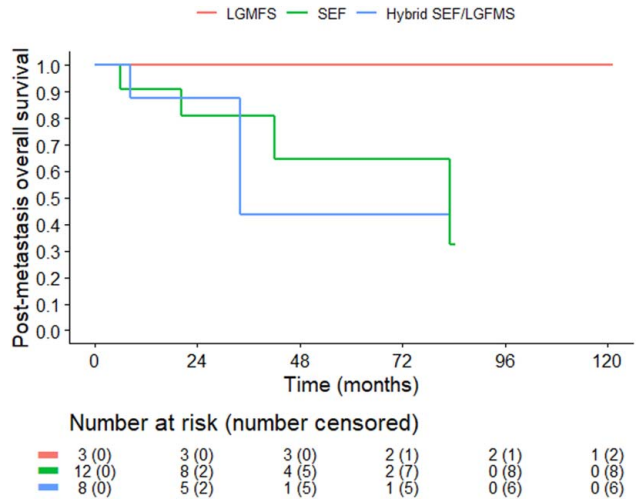

FIGURE 5. Post-metastases overall survival according to histologic subtype. The graph represents the overall survival in patients who had a distant metastasis. Patients in the LGFMS subgroup who had an event (Fig. 3) are not represented in this curve because they did not have DM. LGFMS indicates low-grade fibromyxoid sarcoma; SEF; sclerosing epithelioid fibrosarcoma.

alteration involving *FUS* and *EWSR1* genes, in particular 62% (8 patients) had positive *FUS* rearrangements and 31% (4 patients) *EWSR1::CREB3L1* gene fusion. Comparing these 2 small subsets of H-LGFMS/SEF, 3/8 (37.5%) *FUS*-positive and 3/4 (75%) *EWSR1*-positive patients developed DM, with 3-year estimate DM of 37.5% (CI: 10.5-100) and 66.7% (CI: 22.3-100), respectively. In another series, including 8 cases from Memorial Sloan-Kettering Cancer Center, all H-LGFMS/SEF exhibited the *FUS::CREB3L2* fusion.[11] While H-LGFMS/SEF and LGFMS both exhibit the *FUS::CREB3L2* fusion, the clinical behavior of H-LGFMS/SEF more closely resembles that of SEF. However, we may speculate that *FUS*-positive H-LGFMS/SEF are less similar to SEF than *EWSR1*-positive H-LGFMS/SEF and test patients at diagnosis to inform management.

An interesting point of discussion is whether H-LGFMS/SEF is one separate entity or, conversely, part of a spectrum with SEF and/or LGFMS. In this study, SEF and H-LGFMS/SEF showed similar clinical behavior with a similar metastatic risk. On the other hand, the analysis of the metastatic series revealed that H-LGFMS/SEF more closely mimicked the behavior of LGFMS. Starting from these preliminary observations, a prospective observational study (also with a translational substudy) is planned to better characterize these 3 entities and the correlation of their outcome with the molecular profile.

In conclusion, this study, along with the French series,[8] helps clarify the natural history of these ultra-rare sarcomas. This study highlights the importance and impact of investigators from multiple institutions and countries coming together to advance the knowledge and treatment of ultra-rare sarcomas. Our data show that localized LGFMS have a high chance of cure with surgery alone, while localized SEF and H-LFGMS/SEF have a more aggressive behavior and higher metastatic risk. Long-term follow-up is essential to assess absolute cure rates and possibly identify prognostic factors.

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