ORIGINAL RESEARCH

Patterns of care and outcomes of 417 patients with METAstatic SYNovial sarcoma (METASYN): real-life data from the French Sarcoma Group (FSG)

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Background: Synovial sarcoma (SS) occurs in both adult and pediatric patients. The primary aim of this study is to describe the outcomes, prognostic factors, and treatment of patients with metastatic SS within a nationwide cohort.
Patients and methods: All pediatric and adult patients with metastatic SS are registered in the French Sarcoma Group database. Data were collected from the national database https://conticabase.sarcomabcb.org/ up to March 2020. Descriptive and comparative analyses were conducted using SAS 9.4 and Stata Special Edition 16.1 software.
Results: Between January 1981 and December 2019, 417 patients with metastatic SS from 17 French sarcoma centers were included, including 64 (15.3%) under the age of 26 years. Median age was 42.5 years (range 9-87 years). The metastases were synchronous (cohort 1) or metachronous (cohort 2) in 18.9% ($N = 79$) and 81.1% ($N = 338$) patients, respectively. Median overall survival (OS) from the date of metastasis was 22.3 months (95% confidence interval 19.7-24.1 months). First-line chemotherapy without ifosfamide and/or doxorubicin was unfavorable for progression-free survival and OS ($P < 0.001$). Concerning cohort 1, young age, surgery of the primary tumor, and single metastatic site were independent favorable prognostic factors for OS. In cohort 2, surgery within an expert French Sarcoma Group center, absence of chemotherapy in the perioperative setting, the lungs as a single metastatic site, time to first metastasis >12 months, local therapy, and ifosfamide in the first metastatic line were independent favorable prognostic factors.
Conclusions: The outcome of patients with metastatic SS is influenced by local treatment, management in reference centers, and cytotoxic treatments given in the perioperative and metastatic setting.
Key words: metastatic synovial sarcoma

INTRODUCTION

Synovial sarcoma (SS) is a malignant mesenchymal tumor characterized by a specific t(X; 18) (p11.2; q11.2) chromosomal translocation with a high risk of metastases that can even occur late, up to 5 years.[1-4] SS represents <3% of cases of soft tissue sarcoma (STS), with an incidence of 1.674/million/year according to recent epidemiological data

from the NetSarc+ network in 2021, but is the most common non-rhabdomyosarcoma in young patients.[5-8] Its second characteristic is a prognosis usually described as worse for adult versus pediatric patients, possibly because of differences in additional somatic genetic rearrangements.[9-11] In terms of prognosis, there are still questions regarding age and the specificities of SS,[6,12-15] such as perioperative treatment. In a metastatic context, ifosfamide and Adriamycin regimens remain the backbone of treatment, but new emerging treatments for SS include regorafenib and T-cell therapy based on *NY-ESO-1* and *MAGE-A4* in selected subgroups of patients.[16-18]

In this context, characterizing the natural history of SS is important, and requires larger series than those previously

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reported. The objective of 'METASYN', a retrospective study by the French Sarcoma Group (FSG), was to describe the management and outcomes of adult and pediatric patients with metastatic SS and included in the Conticabase database.

MATERIAL AND METHODS

Conticabase

The Conticanet database and tumor bank contains anonymized information describing tumors, treatment, and follow-up, as well as tumor sample availability and molecular biology analyses for mesenchymal tumors. The data have been collected thanks to the Conticabase https://conticabase.sarcomabcb.org/ set up in 2005.

Patients

Clinical data were collected from the Conticabase (https://conticabase.sarcomabcb.org) and not from the NetSarc database, which was set up later. The study was first approved by the FSG, then declared to the Commission Nationale de l'Informatique et des Libertés (CNIL) on 18 July 2018, number 2203224, and approved by the ethics committee in Angers on 4 February 2020 (approval number 2020/10). All living patients received an information letter. Clinical data for the 417 patients were updated. Between July 1980 and April 2019, the sex, histology, grade, depth, size, location, treatment, relapse, and survival of the 417 adults, children, and adolescents and young adults (AYA, 15-25 years old) with treated metastatic SS were collected.

Two cohorts of patients were created in 'METASYN': cohort 1 for patients with synchronous metastatic SS, and cohort 2 for patients with metachronous metastatic SS. For the first cohort, the date of diagnosis corresponded to the diagnosis of the metastasis, whereas for the second, the date of diagnosis of the metastasis came after that of the initial diagnosis (range 1-478, median 20 months).

Statistical analysis

All data were anonymized and analyzed retrospectively. Qualitative factors were described by the frequency of their respective modalities and compared using Pearson's chi-square test (or Fisher's exact test). Continuous factors were described by their mean $\pm$ standard deviation (or median—interquartile—range) and compared using Student's t-test (or the Mann—Whitney/Wilcoxon test). The dose intensity of ifosfamide was calculated as the total dose received and the number of courses. Overall survival (OS) was defined as the time from the date of treatment of the first metastatic relapse to the date of death. Progression-free survival (PFS) was defined as the time from the start of the reporting periods to the date of progression (or the date of the next line or the date of death). All survivals were described using Kaplan—Meier curves. Log-rank tests and univariate Cox proportional-hazards analyses were carried out to identify prognostic factors in each cohort. At the final step, and for each cohort separately, the confounding factors were taken into account to assess the independent prognostic impact on OS and PFS of the

parameters studied. Variables with a P value <0.20 at the univariate step were introduced into a semi-parametric multivariate Cox model to calculate adjusted hazard ratios (HR) with their 95% confidence interval (CI). The validity of the final model for proportional hazards was tested. All tests were carried out in a bilateral formulation and the significance limit was set at 5%. All analyses were carried out using SAS 9.4 (SAS Institute Inc., Cary, NC) and Stata Special Edition 16.1 (Stata-Corp, College Station, TX) software.

RESULTS

Patient and tumor characteristics

The Conticabase collected data from 417 patients from 17 FSG centers. NetSarc is the French clinical reference network for soft tissue and visceral sarcomas, implemented in 2010 and approved by the French National Cancer Institute (INCa) in 2014 (28 centers). New patients from other centers, now called 'NetSarc+ centers', could not be included retrospectively. The Conticabase included 1127 patients (56 children, 1071 adults) with SS, of whom 417 (9 children, 408 adults) had metastatic disease between 15 July 1980 and 24 April 2019. Sixty-four (15.3%) children and AYA were identified, of whom nine patients were younger than 18 years old. The median age at metastasis diagnosis was 42.5 years (range: 9-87 years). Patient characteristics are presented in Table 1. Metastases were synchronous for 79/417 (18.9%) patients (cohort 1) and metachronous for 338/417 (81.1%) patients (cohort 2). The primary tumor was located in the limbs, thorax, and pelvis for, respectively, 242/416 (58.2%), 74/416 (17.8%), and 46/416 (11.1%) patients. The lungs were the first location for metastases in 284/373 (76.1%) patients, followed by the lymph nodes 22/373 (5.9%) and pleura 19/373 (5.1%). Mean primary tumor size was 126 ± 50.4 and 79.7 ± 41.5 mm in cohorts 1 and 2, respectively ($P < 0.0001$). No other differences in the tumors were noted between the two cohorts in terms of patient characteristics. Notably, there was no significant difference in age. In cohort 2, relapses occurred 1, 2, 5, and 10 years after the initial diagnosis for 71.7%, 41.7%, 14.3%, and 4.5% of patients, respectively (Supplementary Figure S1, available at https://doi.org/10.1016/j.esmoop.2022.100402). Median follow-up was 6.9 (4.7-11.3) years after diagnosis of the metastasis for the entire cohort.

Treatment

The treatment of the primary tumor is described in Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2022.100402.

General pattern: initial surgery was carried out outside of one of the FSG's expert centers for 200/368 (54.3%) of patients. The R0 resection rate was 148/368 (40.2%) for all patients. The R0 rate was 64.1% when surgery was carried out within the network versus 51.3% outside the network (Fisher's exact $P = 0.049$).

In cohort 1, initial surgery was carried out in 46/79 (58.2%) patients. The R0 rate was 17/46 (37%). In the

Table 1. Characteristics of patients with metastatic synovial sarcoma and treatment of the primary tumor and metastatic disease in cohort 1 (synchronous metastatic disease) and cohort 2 (metachronous metastatic disease)

Patient characteristics	Global	Cohort 1	Cohort 2	P
Sex, n (%)	n = 417	n = 79	n = 338	0.2660 (K)
Male	230 (55.2)	48 (60.8)	182 (53.8)	
Female	187 (44.8)	31 (39.2)	156 (46.2)	
Age at metastasis diagnosis, years, n (%)	n = 417	n = 79	n = 338	0.2476 (S)
Mean ± SD	42.5 ± 15.1	40.7 ± 16.4	42.9 ± 14.8	
≤25	64 (15.3)	17 (21.5)	47 (13.9)	0.0910 (K)
>25	353 (84.7)	62 (78.5)	291 (86.1)	
Years of metastasis diagnosis, n (%)	n = 417	n = 79	n = 338	0.8435 (K)
<2000	118 (28.3)	23 (29.1)	95 (28.1)	
2000-2010	177 (42.4)	35 (44.3)	142 (42.0)	
>2010	122 (29.3)	21 (26.6)	101 (29.9)	
Tumor site, n (%)	n = 416	n = 79	n = 337	0.2378 (F)
Limb	242 (58.2)	48 (60.8)	194 (57.6)	
Thorax	74 (17.8)	16 (20.3)	58 (17.2)	
Pelvis	46 (11.1)	11 (13.9)	35 (10.4)	
Abdomen	25 (6.0)	2 (2.5)	23 (6.8)	
Head and neck	23 (5.5)	1 (1.3)	22 (6.5)	
Trunk wall	6 (1.4)	1 (1.3)	5 (1.5)	
Size, cm, n (%)	n = 371	n = 70	n = 301	<0.0001 (W)
Mean ± SD	88.5 ± 46.9	126 ± 50.4	79.7 ± 41.5	
<5	64 (17.3)	2 (2.9)	62 (20.6)	<0.0001 (F)
≥5	306 (82.5)	68 (97.1)	238 (79.1)	
Single metastatic site, n (%)	n = 373	n = 66	n = 307	0.0401 (F)
Lung	284 (76.1)	55 (83.3)	229 (74.6)	
Lymph node	22 (5.9)	0	22 (7.2)	
Pleura	19 (5.1)	3 (4.6)	16 (5.2)	
Bone	16 (4.3)	3 (4.6)	13 (4.2)	
Peritoneum	11 (2.9)	0	11 (3.6)	
Liver	6 (1.6)	3 (4.6)	3 (1.0)	
Other	15 (4)	2 (3)	13 (4.2)	

Number of patients with available data (n), Chi-square test (K), Fisher exact test (F).
SD, standard deviation.

perioperative setting, radiotherapy was delivered in 33/79 (41.8%).

In cohort 2, initial surgery was carried out in 322/368 (95.3%) patients. The R0 rate was 131/322 (40.7%). In the perioperative setting, radiotherapy was delivered in 227/338 (67.2%) of patients. Some 216/338 (63.9%) patients received perioperative chemotherapy. This chemotherapy was administered in the neoadjuvant setting, adjuvant setting, or both for 71/338 (21%), 103/338 (30.5%), and 26/338 (7.7%) patients respectively. A total of 85/216 (39.4%) of patients received ifosfamide-based chemotherapy.

The treatment of the metastatic disease is described in Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2022.100402. Ninety-nine patients (31.5%) were included in a clinical trial.

First-line treatment. At the first metastatic relapse, 202/417 (48.4%) patients received local treatment of the metastases, with no statistical difference between cohorts. This local treatment included surgery, radiotherapy, and thermal ablation for 157/417 (77.7%), 91/417 (45%), and 34/417 (16.9%) of patients, respectively. Focal treatment was offered mostly to patients with an SS diagnosed 20 years ago: for 63/87 (72.4%), 79/131 (60.3%), and 60/115 (52.2%) patients before 2000, between 2000 and 2010, and after 2010, respectively (P = 0.004). Focal treatment was offered more frequently in cases of late relapse, with a median time

of 19.4 months versus 12 months for patients without focal treatment (P < 0.001). Patients mostly had only one metastatic site 186/202 (92.1%) versus 103/131 (78.6%) (P = 0.001), and the lung was the single metastatic site (P = 0.002), Supplementary Table S3, available at https://doi.org/10.1016/j.esmoop.2022.100402.

As the systemic first-line treatment of metastases, 314/417 (75.3%) patients received chemotherapy, with a median number of 3 lines (range 1-10 lines): 314/417 (75.3%), 244/417 (58.5%), 170/417 (40.8%), and 110/417 (26.4%) patients received 1, 2, 3, and >3 chemotherapy lines. The most frequently administered agent was ifosfamide, given to 216/314 (68.8%) of these metastatic SS patients. A total of 98 patients did not receive ifosfamide; 51 (52%) had already received it in the (neo)adjuvant setting or local relapses.

In cohort 1, ifosfamide was administered with doxorubicin to 29/59 (49.2%) patients. In cohort 2, ifosfamide was administered with doxorubicin to 71/255 (27.8%) patients. Ifosfamide rechallenge was carried out in 30/133 (22.5%) patients in cohort 2.

Further lines of treatment. Local treatment of metastases was carried out in cases of second and third metastatic relapse for 88/417 (21.1%) and 42/417 (10.1%) patients, with no statistical difference between cohorts. As the second line, 27 patients underwent polychemotherapy,

including anthracycline and/or ifosfamide, 18 had another combination of polychemotherapy, 151 had monotherapy: 8 received doxorubicin, 43 received ifosfamide, 39 trabectedin, 24 a tyrosine kinase inhibitor (TKI), and 37 another systemic therapy.

Response to treatment

As the first line for metastases, chemotherapy led to an objective response rate (ORR) of 94/240 (39.2%) for the entire cohort. There was no statistically significant difference between cohorts: the ORR for cohorts 1 and 2 was 50% versus 36.8%, respectively ($P = 0.094$).

In further metastatic lines, chemotherapy led to an ORR of 44/196 (22.4%), 25/120 (20.8%), 11/79 (13.9%), and 5/38 (13.2%) in the second, third, fourth, and fifth lines, respectively, for the entire cohort. In cohort 1, the ORR was 27.3% and 21.9% in the second and third lines. In cohort 2, the ORR was 21.1% and 20.5% in second and third line. There was no statistically significant difference between cohorts. The ORR according to agent and line of treatment is recorded in Supplementary Table S4, available at https://doi.org/10.1016/j.esmoop.2022.100402. The ORR was better for multiregimen chemotherapy and monochemotherapy with ifosfamide.

PFS

Median PFS (mPFS) in a first-line metastatic setting was 6 months [95% confidence interval (CI) 5.26-7.36 months] for the entire cohort, with no statistical difference between cohorts. Ifosfamide combined with doxorubicin or alone provided better PFS than other regimens (Figure 1) (log-rank P value <0.001): 8.5 months (95% CI 7-10.6 months) and 7.7 months (95% CI 5.4-10.4 months), respectively, versus 4 months (95% CI 2.2-7.9 months) for doxorubicin as the single agent. Trabectedin and a TKI yielded an mPFS of 2.6 months (95% CI 1.3-4.1 months) and 4.1 months (95% CI 2.7-5.0 months), respectively (Supplementary Table S5, available at https://doi.org/10.1016/j.esmoop.2022.100402).

For subsequent treatment lines in metastatic settings, mPFS was 4.1 months (95% CI 3.45-4.70 months), 2.8 months (95% CI 2.27-3.12 months), and 2 months (95% CI 1.81-2.29 months) in the second, third, and beyond lines, respectively, for the entire cohort. Focusing on agent, in the second line, mPFS was 4.4 months (95% CI 2.4-6.0 months) for ifosfamide combined with doxorubicin, and 6.3 months (95% CI 4.2-8.0 months) for ifosfamide alone versus 2.1 months (95% CI 0.8-6.5 months) for doxorubicin as the single agent. Trabectedin and TKI yielded a mPFS of 4.3 months (95% CI 1.4-8.9 months) and 4.4 months (95% CI 3.3-5.9 months) in the second line, respectively.

OS and prognostic factors

The 5-year OS rate after the date of diagnosis of the metastasis was 14.8% (95% CI 11.1% to 18.9%) and median OS was 22.3 months (95% CI 19.7-24.1 months) with no difference between cohorts (log-rank P value = 0.69) and similar OS over time [<2000; (2000-2010); >2010] (log-rank P value = 0.62).

In the univariate analysis, favorable prognostic factors for cohort 1 were younger age as a continuous variable, surgery of the primary tumor, R0 margins versus R2 for the resection of the primary tumor, and the lungs as a single metastatic site (Table 2). In cohort 2, for patients who underwent surgery (322/338) (95.3%), favorable prognostic factors included were primary surgery within an expert FSG center, absence of chemotherapy in the perioperative setting, the lung as a single metastatic site, time to first metastasis >12 months, local treatment of the metastasis as the first line, and ifosfamide- and doxorubicin-based chemotherapy as the first metastatic treatment (Table 3).

In the multivariate analysis, younger age, surgery of the primary tumor, and a single metastatic site remained independent favorable prognostic factors for OS in cohort 1 (Table 2). For cohort 2, primary surgery within an expert FSG center, absence of chemotherapy in the perioperative setting, the lung as a single metastatic site, time to first metastasis >12 months, local therapy as the first-line metastatic treatment, and ifosfamide in the first metastatic line were independent favorable prognostic factors (Table 3, Figure 1) (log-rank P value <0.001). The dose intensity of ifosfamide did not translate into improved OS [<9000 mg/m^2, (log-rank P value = 0.059); 9000-12 000 mg/m^2, (log-rank P value = 0.07); 12 000-14 000 mg/m^2, (log-rank P value = 0.19); >14 000 mg/m^2, (log-rank P value = 0.23)]. Even in advanced disease, in the second- or third-line treatment, additional focal treatment of the metastases provided better survival: the mPFS was 24.3 months versus 8.9 months (HR = 0.32, P < 0.001) in second-line and 19.5 months versus 7.7 months (HR = 0.49, P = 0.003) in third-line (Figure 2).

DISCUSSION

To our knowledge, the specific outcome of metastatic SS is not extensively reported in the literature. METASYN reports the FSG experience with one of the largest retrospective studies on metastatic adult and pediatric SS.

For prognostic factors, tumor size, usually observed in series focused on localized SS,[19-22] disappeared in favor of other parameters[23]: few metastases, location in the lungs, and occurrence beyond 1year were significantly linked to better OS in this study, in accordance with the literature.[19-21,24,25] Age as a prognostic factor is a point of debate, as proven in localized SS.[7,12,20,23,26,27] This has been less clearly established in the metastatic setting due to both the low number of studies and the contradictory results that have been observed.[14,19,21,26] In the current study, young age as a continuous variable remained a favorable prognostic factor for synchronous metastatic patients. Beyond age, the genomic profiles of adult and pediatric SS patients backed up the hypothesis of heterogeneity for SS: Complexity Index in Sarcomas (CINSARC) and genomic index show that the adult tumor genome is more frequently rearranged.[9,11]

Concerning routine clinical practice, METASYN shows that surgery of the primary tumor with R0 margins and carried
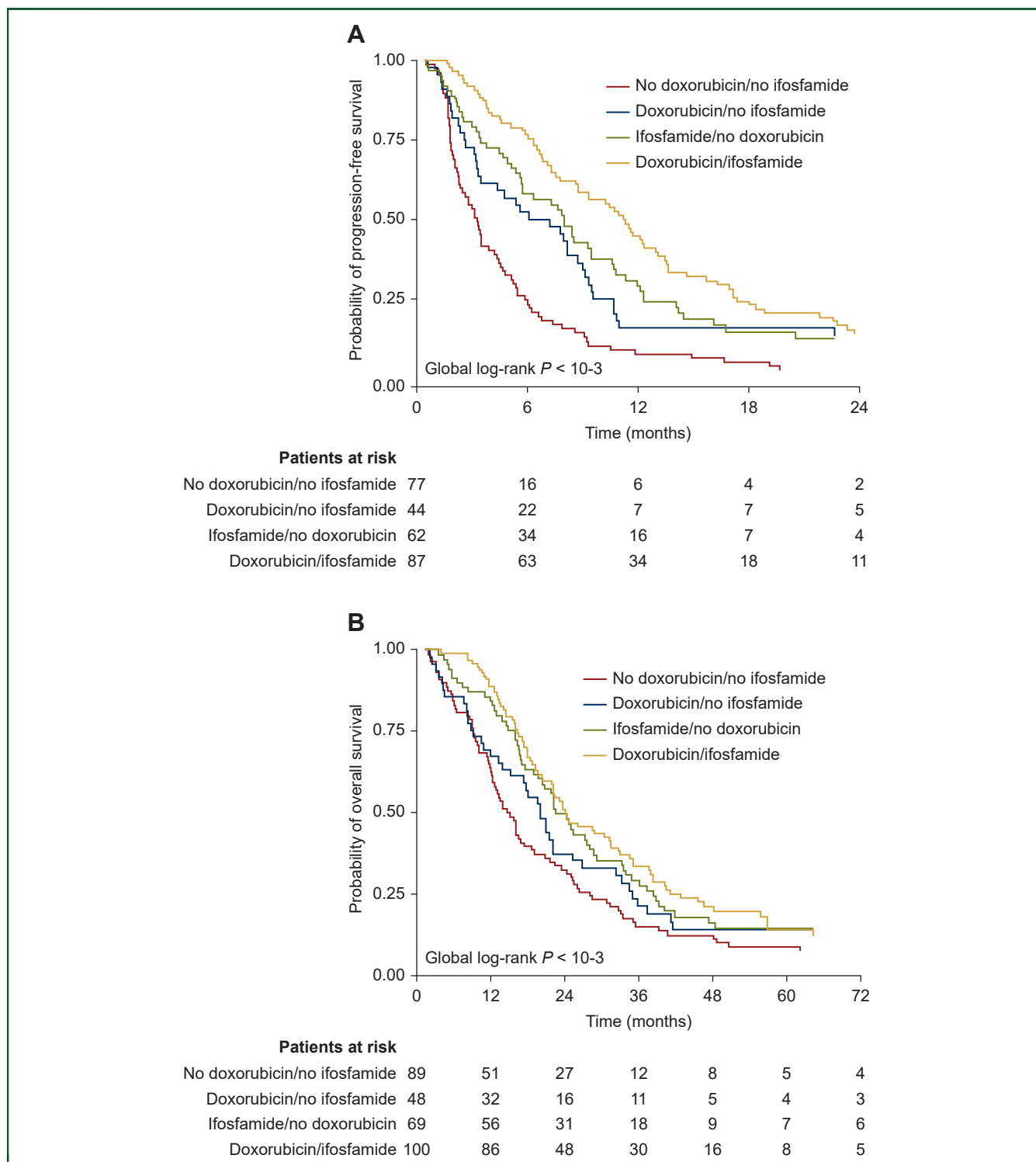
Figure 1. (A) Progression-free survival and (B) overall survival according to first metastatic chemotherapy line.

out in a reference center confers a significant advantage for OS, as well as for patients with *de novo* metastases in multivariate analyses. In the field of oncology, primary tumor surgery in the *de novo* metastatic setting is often debated. The most recent trials on clear-cell renal carcinoma and prostate cancer have led to new guidelines.[28,29] For sarcoma, the literature insists on surgery for local control rather than for survival.[30] Furthermore, the

complexity of the surgery has not made such trials possible. The 'METASYN' results support R0 surgery of the primary tumor being offered in the metastatic setting, especially in young patients with oligometastases, provided that the surgery is reasonable.[21]

For metastases, the value of focal treatment is also debated, with limited evidence-based medicine. Twenty years ago, the Royal Marsden Hospital (RMH) experiment

Table 2. Prognostic factors for overall survival in cohort 1 (synchronous metastatic disease): univariate and multivariate analyses ($n = 79$)

Characteristics	Univariate analysis				Multivariate analysis			
	Hazard ratio	95% CI		P > z	Hazard ratio	95% CI		P > z
Age at diagnosis (continuous variable)	**1.02**	**1.01**	**1.04**	**<0.01**	**1.02**	**1.01**	**1.04**	**<0.01**
Age ≤25 years versus > 25 years old	1.62	0.85	3.07	0.14				
Sex (male versus female)	0.89	0.53	1.50	0.66				
Year of metastasis diagnosis:								
2000-2010 versus <2000	1.51	0.79	2.89	0.21				
>2010 versus <2000	1.62	0.81	3.22	0.17				
Tumor size of primary tumor <50 mm or >50 mm	2.16	0.29	15.9	0.45				
Surgery of the primary tumor yes versus no	**0.53**	**0.31**	**0.90**	**0.02**	**0.58**	**0.34**	**0.99**	**0.04**
Surgeon in network versus extra network ($n = 42$)[a]	0.64	0.31	1.33	0.23				
Margin of primary tumor ($n = 33$)[b]								
R1 versus R0	1.84	0.74	4.59	0.19				
R2 versus R0	**4.19**	**1.05**	**16.7**	**0.04**				
Radiotherapy in perioperative setting versus no	1.04	0.49	2.18	0.93				
Metastatic site:								
Other single versus lung single	**1.74**	**0.81**	**3.76**	**0.15**	**1.90**	**0.88**	**4.15**	**0.10**
Multiple versus lung single	**3.59**	**1.82**	**7.08**	**<0.01**	**3.89**	**1.93**	**7.83**	**<0.01**
Local treatment at first metastatic line	0.64	0.37	1.12	0.12				
Ifosfamide at first metastatic line versus no	0.64	0.35	1.20	0.14				
Doxorubicin at first metastatic line versus no	1.15	0.61	2.20	0.66				

Characteristics that are clinically significant are highlighted in bold. Only age at diagnosis and variables that had a P value of significance <0.10 in the univariate analysis were introduced in the semi-parametric multivariate Cox model.
CI, confidence interval.
[a] Surgery in network versus extra network was not introduced in multivariate analysis due to missing data.
[b] Margin of primary tumor was not introduced in multivariate analysis due to missing data.

revealed no impact of metastasis surgery on survival.[14] Nevertheless, by identifying metastases earlier with an efficient computed tomography scan, focal treatments could be proposed for less advanced disease and probably contribute to this trend. METASYN demonstrates better OS for metastasis surgery in multivariate analysis in accordance with studies dedicated to SS.[19,26,31] Offering focal treatment to selected patients with lung oligometastases, even for synchronous metastases or after several lines of treatment, is a fair option as late relapse is not unusual in SS.[13,15,25,31]

Perioperative chemotherapy is not standard for STS, and European Society for Medical Oncology (ESMO) guidelines do not systematically recommend adjuvant chemotherapy as standard treatment (leaving it to the multidisciplinary tumor board to decide on a case per case basis in view of

Table 3. Prognostic factors for overall survival in cohort 2 with surgery (metachronous metastatic disease): univariate and multivariate analyses ($n = 322$)

Characteristics	Univariate analysis				Multivariate analysis			
	Hazard ratio	95% CI		P > |z|	Hazard ratio	95% CI		P > |z|
Age at metastatic diagnosis (continuous variable)	1.01	0.99	1.01	0.62	1.01	0.99	1.01	0.12
Age ≤25 years versus >25 years old	1.11	0.78	1.58	0.55				
Sex (male versus female)	1.16	0.90	1.49	0.24				
Year of metastasis diagnosis:								
2000-2010 versus <2000	0.80	0.60	1.06	0.12				
>2010 versus <2000	0.82	0.59	1.14	0.23				
Tumor size of primary tumor <50 mm or >50 mm	1.08	0.78	1.50	0.63				
Surgery in network versus extra network	**0.67**	**0.52**	**0.88**	**<0.01**	**0.57**	**0.41**	**0.78**	**<0.01**
Margin of primary tumor ($n = 219$)[a]								
R1 versus R0	1.28	0.92	1.76	0.14				
R2 versus R0	1.69	0.98	2.92	0.06				
Radiotherapy in perioperative setting versus no	0.81	0.20	3.34	0.77				
Chemotherapy in perioperative setting versus no	1.26	0.98	1.63	0.07	**1.56**	**1.08**	**2.26**	**0.02**
Metastatic site:								
Other single versus lung single	**1.58**	**1.13**	**2.22**	**<0.01**	**1.67**	**1.16**	**2.41**	**<0.01**
Multiple versus lung single	**3.44**	**2.18**	**5.43**	**<0.01**	**2.17**	**1.32**	**3.57**	**<0.01**
Time to first metastasis >12 months versus <12 months	**0.45**	**0.34**	**0.60**	**<0.01**	**0.36**	**0.25**	**0.52**	**<0.01**
Local treatment at first metastatic line	**0.34**	**0.25**	**0.45**	**<0.01**	**0.40**	**0.29**	**0.57**	**<0.01**
Ifosfamide at first metastatic line versus no ($n = 236$)	**0.64**	**0.48**	**0.84**	**<0.01**	**0.69**	**0.51**	**0.93**	**0.02**
Doxorubicin at first metastatic line versus no ($n = 236$)	**0.68**	**0.52**	**0.90**	**0.006**	0.75	0.52	1.08	0.12

Characteristics that are clinically significant are highlighted in bold.
Only age at metastatic diagnosis and variables that had a P value of significance <0.10 in the univariate analysis were introduced in the semi-parametric multivariate Cox model.
CI, confidence interval.
[a] Margin of primary tumor was not introduced in multivariate analysis due to missing data.
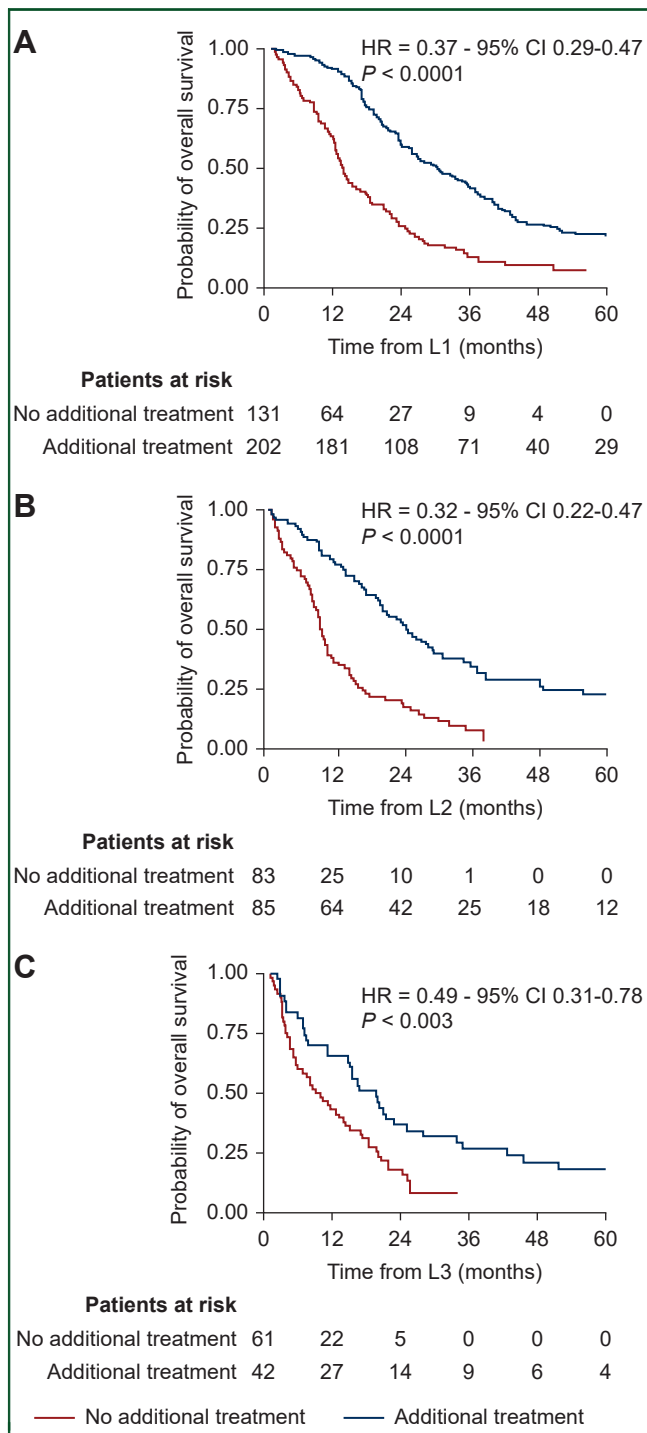
Figure 2. Overall survival for (A) first-line, (B) second-line, and (C) third-line treatments of metastases depending on additional focal treatment.
CI, confidence interval; HR, hazard ratio.

insufficient evidence).[32-38] For SS, chemotherapy is a debated moot point too.[19,20,39,40] There are not enough prospective studies for this rare histotype, and the most representative is the ISG-STS 1001 trial: no superiority for histotype-tailored chemotherapy was reported, but caution is needed when interpreting the results: standard treatment made possible better PFS and OS for certain patients, with a high risk of metastasis.[37,41]

METASYN shows that chemotherapy in a (neo)adjuvant setting is associated with worse survival in multivariate analyses. For patients treated with ifosfamide as the first line for the metastases, mPFS was similar whether or not they had received ifosfamide in a (neo)adjuvant setting ($P =$ 0.80). The retrospective nature of this study obviously makes it prone to bias, here related to the aggressiveness of the disease. Histological data with monophasic or biphasic subtypes or fusion partners (SS1, SS2) were not available. As a result of all this, absolutely no conclusions can be drawn.

In this context, the FSG's decision is to carry on working to better define the role of adjuvant chemotherapy, and a further step is ongoing with a new prognostic tool, the CINSARC signature,[9,10] incorporated into several trials in the NetSarc network in an adjuvant setting (CHIC-STS01, CIR-SARC).[42-46] For the first results in high-risk STS patients treated with preoperative chemotherapy with radio-chemotherapy, CINSARC did not correlate with different disease-free survival and OS. While this may well be due to a failure of this specific gene signature in this specific patient population, an alternative hypothesis is that preoperative chemotherapy may improve the prognosis of higher-risk patients.[47]

In the metastatic setting, METASYN shows that ifosfamide-based chemotherapy is still the backbone of treatment, with the well-known chemosensitivity of SS,[14,48-53] and yields superior ORR, PFS, and OS even without dose dense intensity. In METASYN, no link between dose dense intensity and survival was observed. Nevertheless, in this retrospective study, only the initial schedule was observed and not any potential dose reduction. As proposed in the clinical practice guidelines,[36] the METASYN results support using multiagent chemotherapy with ifosfamide for selected patients with symptoms and oligometastatic disease as part of a multidisciplinary approach.[33,54] METASYN confirms the chemosensitivity of SS beyond the first line, as already demonstrated with a rechallenge of both ifosfamide and other agents.[14,15,48] Trabectedin is used in more than a quarter of responders as the third line according to series that reported objective responses and high rates of stable disease (30%-50%), even for heavily pretreated patients, with OS ranging between 9 and 13 months. Trabectedin should be an option for certain patients with SS, even if better results are obtained in L-sarcomas.[50,55-65] TKIs for SS appear to be another major treatment in METASYN, with mPFS equal to 4.4 months. Since 2009, TKIs have demonstrated activity with pazopanib with a 49% 3-month PFS rate,[66] and later on in PALETTE with better PFS for leiomyosarcomas and SS, and with regorafenib in REGOSARC with an mPFS of 5.6 months.[16,67] Finally, new agents have emerged thanks to active research and identification of immunogenic antigens (NY-ESO-1 and *MAGE-A4*) frequently expressed on SS.[68,69] After the initial disappointment with anti-programmed cell death protein 1 immunotherapy, 11% and 0% partial responses in the SARC 028 and ALLIANCE A091401 trials, respectively, promising data have been reported recently.[70-72] A phase I trial by the *Memorial Sloan Kettering Cancer Center* (MSKCC) with letetresgene, an

NY-ESO-1-specific T-cell receptor T-cell therapy, reported significant results: 50% ORR, mPFS of 15 months, and median OS of 24 months for heavily pretreated patients.[17] The MD Anderson Cancer Center carried out another phase I trial with ADP-A2M4 T-cell therapy for MAGE-A4+ SS, obtaining impressive results: 44% ORR and mPFS of 20 weeks.[17,18,72] These trials are currently in progress.

In the METASYN study, 34/339 (10%) patients were alive after 5 years. The clinical parameters for longer survival included metachronous metastases ($P = 0.057$), younger patients ($P = 0.039$), few metastases ($P = 0.02$), and lung location ($P = 0.004$). Treatment parameters significantly linked to this longer survival were: surgery of the primary tumor ($P = 0.021$), surgery in a NetSarc center ($P = 0.036$), and focal treatment of metastases ($P < 0.001$).

The fact that patient records are kept over a long period of time, in our case almost 40 years, is always questionable because of classification and treatment changes over time, although this does not apply to SS, and for a rare histotype it is relatively common.[14,20,26,27] The positive effect of time is that it is possible to make comparisons across periods in real life. First of all, METASYN reports the same clinical characteristics across various periods and countries: synchronous metastases for a quarter of the patients, limbs as the main site,[14,20,21,73] primary tumor size of >5 cm,[14,20,21,73] especially in patients with synchronous metastases,[20-22,74] and the lungs as the usual metastatic site.[14,20,21] The second criticism is that the FSG database includes data for all patients but because the size of the cohorts was too small between children and adults, the differences in clinical presentation could not be shown. In published series, mostly focused on patients with localized SS, no difference has been observed, even if a trend has been identified in the literature with a higher proportion of locations in the thigh, large invasive tumors, and an increased risk of synchronous metastases for AYA in comparison to children.[7,26,27] Third, and because of the retrospective nature of METASYN, caution is needed when evaluating the response rate as there was probably not always a RECIST reference or a centralized radiological review. Nevertheless, these results provide a trend for agents and that is useful in SS in real life, with ifosfamide and secondly TKIs and trabectedin as benchmarks for new agents. So far, few studies have provided a response rate for one sarcoma subtype in several lines outside of trials.[15,16] The same comment can be made with regard to PFS, again with caution in the interpretation. Nevertheless, the mPFS in first-line treatment with ifosfamide, 6-7 months, seems close to the mPFS in other series.[15,75] Finally, METASYN provides median OS and 5-year OS of 22 months and 14.8%, which is quite similar to previous series with median OS between 15 and 22 months.[13-15,49,65,75] This helps us feel confident with these results. With a long recruitment period, METASYN shows no improvement across periods and emphasizes the unmet need for new agents in SS. Survival was better than the OS in the EORTC trials[15]; perhaps administering several lines with new agents, even 'off-label', contributed to a survival advantage in METASYN.

This is quite interesting, and once again similar to previous studies. It demonstrates that a survival advantage through the choice of polychemotherapy as the first line had to be stated for medical practice in the specific cases mentioned above.[15,65,75] The lack of power in the latest EORTC trial in the first line, A versus AI, may explain the different conclusion.[54] Monotherapy should nevertheless always be considered in palliative sarcoma cases with very poor prognosis as a means of improving quality of life.[54]

Conclusion

This new study by the Conticabase network confirms that surgery is the mainstay treatment in reference centers for improving OS. METASYN emphasizes the importance for OS of focal treatment of metastases. (Neo)adjuvant treatment has undoubtedly been a never-ending moot point and patients need to be enrolled in the current clinical trial based on the CINSARC signature. Finally, this study offers real-life results in a metastatic setting and is a useful support for developing promising new strategies.

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