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Sarcomas in patients over 90: Natural history and treatment—A nationwide study over 6 years

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Abbreviations: LMS: leiomyosarcomas; MDT: multidisciplinary team; MFS: myxofibrosarcomas; PFS: progression-free survival; STS: soft tissue sarcomas; UPS: undifferentiated pleomorphic sarcomas

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Soft tissue sarcomas (STS) are rare tumors accounting for less than 1% of human cancers. While the highest incidence of sarcomas is observed in elderly, this population is often excluded or poorly represented in clinical trials. The present study reports on clinicopathological presentation, and outcome of sarcoma patients over 90 recorded in the Netsarc.org French national database. NETSARC (netsarc.org) is a network of 26 reference sarcoma centers with specialized multidisciplinary tumor board (MDTB), funded by the French National Cancer Institute to improve the outcome of sarcoma patients. Since 2010, presentation to an MDTB, second pathological review, and collection of sarcoma patient characteristics and follow-up are collected in a database. Information of patients registered from January 1, 2010, to December 31, 2016, in NETSARC were collected, analyzed and compared to the younger population. Patients with sarcomas aged >90 have almost exclusively sarcomas with complex genomics (92.0% vs. 66.3%), are less frequently metastatic (5.3% vs. 14.7%) at diagnosis, have more often superficial tumors (39.8% vs. 14.7%), as well as limbs and head and neck sites (75.2% vs. 38.7%) (all $p < 0.001$). Optimal diagnostic procedures and surgery were less frequently performed in patients over 90 ($p < 0.001$). These patients were less frequently operated in NETSARC centers, as compared to those of younger age groups including aged 80–90. However, local relapse-free survival, metastatic relapse-free survival and relapse-free survival were not significantly different from those of younger patients, in the whole cohort, as well as in the subgroup of operated patients. As expected overall survival was worse in patients over 90 ($p < 0.001$). Patients over 90 who were not operated had worse overall survival than younger patients (9.9 vs. 27.3 months, $p < 0.001$). Patients with STS diagnosed after 90 have distinct clinicopathological features, but comparable relapse-free survival, unless clinical practice guidelines recommendations are not applied. Standard management should be proposed to these patients if oncogeriatric status allows.

What's new?

While the highest incidence of soft-tissue sarcoma (STS) is observed in the elderly, this population is often excluded or poorly represented in clinical trials. Therefore, little is known about the characteristics, treatment, and outcomes of STS in these patients. In this study, the authors analyzed numerous clinical characteristics of patients with sarcoma diagnosed at age 91 or older. They conclude that standard STS management and clinical practice guidelines should be followed for these patients if possible.

Introduction

Soft tissue sarcomas (STS) are rare tumors accounting for less than 1% of human cancers, with a yearly incidence close to 5.9/100,000.^{1–5} Death due to tumor is frequent in this group of diseases.⁵ While the highest incidence of sarcomas is observed in patients aged between 75 and 84 years with a rate of 16%,^{1,5} elderly patients are often excluded or very poorly represented in clinical trials.⁶ Therefore, little is known about characteristics, treatment and outcomes concerning patients aged over 65, in particular for those over 90 years with STS.^{6,7}

Sarcomas represent a heterogeneous group with over 80 different pathological subtypes.⁸ Sarcoma with “simple genomics” include those with specific translocations, well-differentiated liposarcomas with 12q amplicon and GIST with tyrosine kinase mutation accounting for 12–20% of cases each; those with “complex genomic” profiles (e.g., undifferentiated pleomorphic sarcomas [UPS], leiomyosarcomas [LMS] and myxofibrosarcomas [MFS]) account for 50% of all STS.^{9–11}

The objective of this work was to analyze the presentation and outcome of sarcoma patients over 90 years, a group of patients unreported in the literature, with the aim of providing data which could guide the management of the general elderly patient population with sarcomas.

Patients and Methods

NETSARC network

NETSARC is the French reference network for the management of soft tissue and visceral sarcomas, collecting clinical, centrally reviewed pathology, therapeutics and outcome of all sarcoma patients in 26 centers. The registry was approved in October 2009 by the INCa (Institut National du Cancer) and the competent authorities (CNIL) in 2010.⁵ These databases have been approved by the French Ethics Committee and Agency in charge of noninterventional trials: Comité consultatif sur le traitement de l'information en matière de recherche dans le domaine de la Santé (CCTIRS: number of approval 09.594) and Commission Nationale Informatique et Liberté (CNIL: number of approval 909,510). In the present work, we used information of patients registered from January 1, 2010, to December 2016. Mean follow-up of this series is 17 months. Patient's data (gender, histology, grade, depth, size, localization, treatment, relapse and survival) were collected from the NETSARC database (<https://netsarc.org>).

Statistical analysis

Collected data were analyzed using IBM SPSS Statistics version 20 (IBM, Paris, France). Chi-square and Fisher exact tests were

Table 1. Patient characteristics

	Age at diagnosis		<i>p</i>
	Diagnosis at ≤90 <i>n</i> (%) <i>n</i> = 12,722 (99.4%)	Diagnosis at >90 <i>n</i> (%) <i>n</i> = 113 (0.6%)	
Age at diagnosis (years)			
Median	62	92	
Range	0–90	91–101	
Sex			
Female	6,283 (49.4%)	62 (54.9%)	NS ¹
Male	6,439 (50.6%)	51 (45.1%)	
Localization at diagnosis			
Trunk	6,706 (52.7%)	25 (22.1%)	≤0.001 ¹
Limb	4,218 (33.2%)	67 (59.3%)	
<i>Superior limb</i>	1,092 (8.6%)	22 (19.5%)	
<i>Inferior limb</i>	3,126 (2.6%)	45 (3.8%)	
Head & neck	710 (5.5%)	18 (15.9%)	
Unknown	1,088 (8.6%)	3 (2.7%)	
Histology			
<i>Complex genomics</i>	8,431 (66.3%)	104 (92.0%)	≤0.001 ¹
UPS	1,569 (12.3%)	40 (35.4%)	
LMS	2,762 (21.7%)	16 (14.2%)	
Myxofibrosarcoma	804 (6.3%)	14 (12.4%)	
Angiosarcoma	666 (5.2%)	12 (10.6%)	
DDLPS	1,506 (11.8%)	11 (9.7%)	
Undifferentiated sarcoma	768 (6.0%)	10 (8.8%)	
Rhabdomyosarcoma	98 (0.7%)	1 (0.9%)	
Fibrosarcoma	44 (0.3%)	0 (0%)	
Liposarcoma pleomorphic	174 (1.4%)	0 (0%)	
Osteosarcoma	40 (0%)	0 (0%)	
<i>GIST</i>	1,490 (11.7%)	6 (5.3%)	
<i>Translocation sarcoma</i>	2,801 (22.0%)	3 (2.7%)	
Ewing	769 (6.0%)	1 (0.9%)	
Myxoid LPS	484 (3.8%)	1 (0.9%)	
Synovial sarcoma	635 (5.0%)	1 (0.9%)	
ESS	273 (2.1%)	0 (0%)	
Epithelioid hemangioendothelioma	100 (0.9%)	0 (0%)	
EMC	89 (0.7%)	0 (0%)	
SFT	451 (3.5%)	0 (0%)	
Grade			
1	1,086 (8.5%)	6 (5.3%)	NS ¹
2	3,133 (24.6%)	24 (2.2%)	
3	3,800 (29.9%)	39 (34.5%)	
Unknown	4,703 (36.9%)	44 (38.9%)	
Depth			
Superficial	1,873 (14.7%)	45 (39.8%)	<0.001 ¹
Deep	8,636 (67.9%)	50 (44.2%)	
Superficial + deep	806 (6.3%)	13 (11.5%)	
Unknown	1,407 (11.1%)	5 (4.4%)	
Size			
<50 mm	1,620 (12.7%)	18 (15.9%)	NS ¹

(Continues)

Table 1. Patient characteristics (Continued)

	Age at diagnosis		<i>p</i>
	Diagnosis at ≤90 <i>n</i> (%) <i>n</i> = 12,722 (99.4%)	Diagnosis at >90 <i>n</i> (%) <i>n</i> = 113 (0.6%)	
≥50 mm	3,924 (30.8%)	29 (25.7%)	
Unknown	7,178 (56.4%)	66 (58.4%)	
Previous history of radiotherapy			NS ¹
No	12,388 (97.7%)	110 (97.3%)	
Yes	294 (2.3%)	3 (2.7%)	
Previous history of cancer			NS ¹
No	8,563 (67.3%)	68 (60.2%)	
Yes	1,741 (13.7%)	20 (17.7%)	
Unknown	2,418 (19.0%)	25 (22.1%)	
Known genetic predisposition			NS ¹
No	10,181 (80.0%)	88 (77.9%)	
Yes	123 (1.0%)	0 (0%)	
Unknown	2,418 (19.0%)	25 (2.1%)	
Metastatic at diagnosis			0.009 ¹
Yes	1865 (14.7%)	6 (5.3%)	
No	9,664 (76.0%)	89 (78.8%)	
Unknown	1,193 (9.4%)	18 (15.9%)	

Italics refer to molecular subtypes of sarcomas.

¹Chi² test.

performed to analyze the data sets of the different age groups. Survival was plotted according to the Kaplan–Meier method, compared to the log-rank test. Cox model was used for multivariate analysis of prognostic factors.

Results

Population

A total of 12,835 incident patients with sarcomas, with 113 (0.9%) patients aged >90 were registered in the national NETSARC sarcoma database between January 1, 2010, and December 31, 2016. Patients' characteristics are described in Table 1. Sarcomas with complex genomics were overrepresented in patients over 90 when compared to patients under 90 (92.0% vs. 66.3%, $p < 0.001$). Undifferentiated pleomorphic sarcoma (UPS), LMS and MFS were the most represented histological subtypes in patients over 90 (Table 1). Limb and head and neck sites, and superficial locations were overrepresented in patients over 90 ($p \leq 0.001$). Male patients were overrepresented in patients aged >90 while representing close to 25% of French citizen aged >90.

(<https://www.insee.fr/fr/statistiques/1892086?sommaire=1912926>), male patients represented 45% of the patients in this age group. Patients >90 were also less frequently metastatic at initial diagnosis ($p = 0.009$), even when considering only patients who had a CT scan (data not shown). Prior history of cancers and radiotherapy were no more frequent in patients aged over 90 vs. younger patients (Table 1). Genetic predisposition was observed in none of the 113 patients over 90 vs. 123 reported in the remaining population.

Patient management

The adherence to ESMO clinical practice guidelines (2,3) was then analyzed (Table 2). While biopsy rate was similar, patients aged over 90 had less frequently appropriate pretreatment imaging than patients under 90 (56.6% vs. 75.1%, $p \leq 0.001$). This was true also when comparing patients aged >90 to the group of 60–80 or 80–90 (Table 3).

Surgery was less frequently performed in patients over 90 years (60.2% vs. 78.3%, $p \leq 0.001$); they also had less frequently neoadjuvant treatment. This did not result in significant differences in terms of resection margins at first or at second surgery (Table 2). Resection rates (Table 2) and final result of the surgical removal (Table 3) were also not significantly different when comparing only patients for whom the R criterion was documented.

Patients over 90 as compared to other age groups

Table 3 presents an analytic description of histologies, clinical presentations and management within different age subgroups. As expected, histological subtypes were extremely different across age groups, in particular across the extremes. It is interesting to note that differences were also observed in the three elder groups, on histologies, depth, grade and metastasis. As compared to the 80–90 years group, histotypes, depth, metastasis at diagnosis and gender of patient with sarcoma aged >90 were different (Table 3). Regarding patient management, compliance to CPGs was the lowest in patients aged >90, together with the final quality of surgery (lowest R0 rate, highest R2 rate), with fewer patients operated in reference centers. Overall a significant trend

Table 2. Disease management in patients aged above and under 90

	Age at diagnosis		<i>p</i>
	Diagnosis at ≤90 <i>n</i> (%) <i>n</i> = 12,712	Diagnosis at >90 <i>n</i> (%) <i>n</i> = 113	
<i>Disease management</i>			
Biopsy performed before surgery			NS ¹
Yes	8,213 (64.6%)	72 (63.7%)	
No	3,552 (27.9%)	32 (28.3%)	
Unknown	957 (7.5%)	9 (8.0%)	
Imaging performed before surgery			≤0.001 ¹
Yes	9,552 (75.1%)	64 (56.6%)	
No	700 (5.5%)	14 (12.4%)	
Unknown	2,470 (19.4%)	35 (31.0%)	
Neoadjuvant treatment before surgery			0.045 ¹
Yes	835/3565 (23.4%)	3/34 (8.8%)	
No	2730/3565 (76.6%)	31/34 (91.2%)	
Total	3,565	34	
Surgery performed			≤0.001 ¹
Yes	9,988 (78.5%)	68 (60.2%)	
No	1,014 (8.0%)	23 (20.4%)	
Unknown	1,720 (13.5%)	22 (19.5%)	
Excision margins of first surgery			0.09 ¹
R0	3,910 (30.7%)	26 (23%)	
R1	2,608 (20.5%)	20 (17.7%)	
R2	990 (7.8%)	9 (8%)	
Unknown	5,214 (41.0%)	58 (51.3%)	
Reexcision after first surgery			NS ¹
No	11,380 (89.5%)	105 (92.9%)	
Yes	1,342 (10.5%)	8 (7.1%)	
Excision margins at second surgery			NS ¹
R0	993 (7.8%)	5 (4.4%)	
R1	213 (1.7%)	2 (1.8%)	
R2	39 (0.3%)	0	
Unknown	97/1342	1/8	

¹Chi-square or Fisher's exact test.

of decrease of compliance to guidelines, management in reference centers and final quality of surgery over age groups was observed, from the children and adolescent/young adults to the older age group (Table 3).

Relapse and survival

Local progression-free survival (PFS), metastatic PFS and PFS were not significantly different in the two populations (Figs. 1a–1c). Relapse-free survival of patients aged over 90 vs. those aged 90 or under was also similar when the analysis was conducted only with operated patients (Fig. 1d). No difference was observed either for local relapse-free survival not for metastatic relapse-free survival for operated patients (data not

shown). As expected, overall survival was worse in patients >90 (Fig. 1e). Importantly, the overall survival of patients who were not operated was significantly worse in patients aged over 90 vs. younger patients (9.9 vs. 27.1 months, $p < 0.001$) with no patient alive at 3 years in the older group vs. 40% in the younger one (Fig. 1f). Using Cox model, with grade, size, depth, site, gender, presentation to a multidisciplinary team (MDT) prior to treatment⁵ and surgery in expert center¹² and age >90 as tested variables, age >90 was not identified as an independent prognostic factor for either relapse-free survival or PFS (data not shown).

Discussion

This analysis of a 6-year nationwide registry of incident sarcoma patients includes over 12,000 patients with 113 (0.9%) patients aged >90. It identifies for the first time-specific pathological and clinical characteristics of sarcomas diagnosed in patients over 90: these are almost exclusively sarcomas with complex genomics, more frequently superficial tumors, from limb sites or head and neck sites. Despite an obvious difference in life duration, sarcoma patients aged over 90 do not have a higher frequency of previous radiotherapy, previous cancers, and none genetic predisposing condition. Patients aged over 90 are also less frequently metastatic at initial presentation than the younger sarcoma patient population and relative to the sex ratio at this age in the French population, more frequently males. These clinicopathological and clinical specificities of sarcomas occurring at an older age are unexpected and had not been previously recognized to our knowledge. It is interesting to observe that these characteristics are not equally shared by the groups aged 60–80 or 80–90, but quite characteristic of this age group. Sarcomas occurring in higher age may result in more from accumulation of external oncogenic events over the lifetime; limb and head and neck sites may suggest exposure to the sun as risk factors to be tested. It is particularly notable that less than 3% of sarcoma in this population was translocation-related sarcomas.

Less adequate management is offered to patients with STS over 90, in particular regarding pretreatment imaging and surgery. Of note, oncogeriatric assessment¹³ is not part of the NETSARC data set, and it is likely that coexisting conditions have largely contributed to these differences with younger patients. However, when patients over 90 are treated with surgery according to clinical practice guidelines (within NETSARC, the ESMO guidelines are used as reference),^{2,3} relapse-free survival and PFS remain similar to that of the younger population in univariate and also multivariate analysis where classical prognostic factors are introduced.^{2,3,5} This points to the need not to under-treat patients, including those aged over 90, and to adopt the classical CPGs for sarcoma management in patients at all age when oncogeriatric status allows. As expected, the overall survival of sarcoma patients aged over 90 is shorter than that of younger patients. Median overall survival is 25 months in this population of patients over 90 (whose median age is 92), an outcome which

Table 3. Sarcoma patient characteristics and management across age groups

Age	Age at diagnosis (% of the age groups within the series)					p value ¹
	0-17 n = 367 (2.9%)	18-30 n = 772 (6.0%)	31-60 n = 4,451 (34.7%)	61-79 n = 5,789 (45.1%)	80-90 n = 1,343 (10.5%)	
Histology						
Complex genomics						
UPS	2 (0.5%)	23 (2.9%)	427 (9.6%)	774 (13.4%)	273 (20.3%)	40 (35.4%)
LMS	7 (1.9%)	44 (5.7%)	1,038 (23.3%)	1,359 (23.5%)	314 (23.4%)	16 (14.2%)
Myxofibrosarcoma	2 (0.5%)	8 (1.0%)	214 (4.8%)	445 (7.7%)	135 (10.1%)	14 (12.4%)
Angiosarcoma	8 (2.2%)	35 (4.5%)	194 (4.4%)	324 (5.6%)	105 (7.8%)	12 (10.6%)
DDLPS	0 (0%)	10 (1.3%)	412 (9.3%)	892 (15.4%)	192 (14.3%)	11 (9.7%)
Undifferentiated sarcoma	11 (2.9%)	40 (5.2%)	245 (13.2%)	369 (6.4%)	103 (7.7%)	10 (8.8%)
Pleomorphic RMS	0 (0.0%)	6 (0.8%)	23 (0.7%)	32 (0.5%)	6 (0.4%)	1 (0.9%)
G/ST	2 (0.5%)	20 (2.6%)	496 (11.1%)	859 (14.8%)	113 (8.4%)	6 (5.3%)
Translocation sarcoma						
Ewing	85 (23.2%)	94 (12.2%)	93 (2.1%)	34 (0.5%)	5 (0.4%)	1 (0.9%)
Myxoid LPS	7 (1.9%)	61 (7.9%)	307 (6.8%)	99 (1.7%)	10 (0.7%)	1 (0.9%)
Synovial sarcoma	39 (10.6%)	144 (18.6%)	322 (7.2%)	114 (1.9%)	16 (1.2%)	1 (0.9%)
Other/not specified	203 (55.3%)	287 (37.2%)	1,080 (24.2%)	488 (8.4%)	71 (5.3%)	0 (0%)
Gender						
Female	153 (41.7%)	362 (46.9%)	2,355 (52.9%)	2,759 (47.7%)	654 (48.7%)	62 (54.9%)
Male	214 (58.3%)	410 (51.3%)	2,096 (47.1%)	3,030 (52.3%)	689 (51.3%)	51 (45.1%)
Grade						
1	9 (2.5%)	68 (8.8%)	513 (11.5%)	418 (7.2%)	78 (5.8%)	6 (5.3%)
2	28 (7.6%)	130 (16.8%)	1,081 (24.3%)	1,541 (26.6%)	353 (26.3%)	24 (21.2%)
3	136 (37.1%)	195 (25.3%)	1,219 (27.4%)	1,735 (30.0%)	515 (38.3%)	39 (34.5%)
UNK/NA	194 (52.8%)	379 (49.1%)	1,638 (36.8%)	2,095 (36.2%)	397 (29.6%)	44 (38.9%)
Depth						
Deep	176 (47.9%)	488 (63.2%)	3,523 (79.2%)	4,361 (75.3%)	894 (66.5%)	63 (55.7%)
Superficial	15 (4.1%)	70 (9.1%)	543 (12.2%)	896 (15.5%)	349 (26.0%)	45 (39.8%)
Unknown	176 (48.0%)	214 (27.7%)	385 (8.6%)	532 (9.2%)	240 (17.8%)	5 (4.4%)
Size in mm (median)	69.1	72.7	70.2	75.5	69.7	8.0
Metastatic at diagnosis						
Yes	96 (26.1%)	155 (20.1%)	658 (14.7%)	831 (14.3%)	146 (10.8%)	6 (5.3%)
No	233 (63.5%)	557 (72.2%)	3,406 (76.5%)	4,430 (76.5%)	1,038 (77.3%)	89 (78.8%)
Unknown	38 (10.4%)	60 (7.8%)	387 (8.7%)	528 (9.1%)	159 (11.8%)	18 (15.9%)

(Continues)

Table 3. Sarcoma patient characteristics and management across age groups (Continued)

Age	Age at diagnosis (% of the age groups within the series)						p value ¹
	0-17 n = 367 (2.9%)	18-30 n = 772 (6.0%)	31-60 n = 4,451 (34.7%)	61-79 n = 5,789 (45.1%)	80-90 n = 1,343 (10.5%)	>90 n = 113 (0.6%)	
Biopsy before							
Yes	299 (81.5%)	555 (71.9%)	763 (62.1%)	3,690 (63.7%)	906 (87.5%)	72 (63.7%)	<0.001
No	35 (9.5%)	162 (21.0%)	1,365 (30.7%)	1,644 (28.4%)	346 (25.8%)	32 (28.3%)	
Unknown	33 (9.0%)	55 (7.1%)	323 (7.3%)	455 (7.9%)	91 (6.8%)	9 (8.0%)	
Imaging < surgery							
Yes	311 (84.7%)	639 (82.8%)	3,406 (76.5%)	4,281 (74.0%)	915 (68.1%)	64 (66.6%)	<0.001
No	8 (2.2%)	29 (3.8%)	199 (4.5%)	326 (5.8%)	128 (9.5%)	14 (12.4%)	
Unknown	48 (13.1%)	104 (13.5%)	846 (19.0%)	1,172 (20.2%)	300 (22.3%)	35 (31.0%)	
Neoadjuvant treat							
Yes	82 (22.3%)	82 (10.6%)	310 (7.0%)	325 (5.6%)	36 (2.7%)	3 (2.7%)	<0.001
No	25 (6.8%)	139 (18.0%)	981 (22.0%)	1,308 (22.6%)	277 (20.6%)	31 (27.4%)	
Total	260 (70.8%)	551 (71.4%)	3,160 (71.0%)	4,156 (71.8%)	1,030 (76.7%)	79 (69.9%)	
Surgery in NETSARC							
Yes	146 (39.8%)	291 (37.7%)	1,529 (34.4%)	1,849 (31.9%)	351 (26.1%)	16 (14.2%)	<0.001
No/No surgery/LUNK	221 (60.2%)	481 (62.3%)	2,922 (65.6%)	3,940 (68.1%)	992 (73.9%)	97 (85.8%)	
Excision margins of last surgery							
R0	122 (33.2%)	307 (39.8%)	1,799 (40.4%)	2,229 (38.5%)	392 (29.2%)	29 (25.7%)	<0.001
R1	47 (12.5%)	105 (13.6%)	721 (16.2%)	997 (17.2%)	254 (18.9%)	18 (15.9%)	
R2	9 (2.5%)	42 (5.4%)	197 (4.4%)	235 (4.1%)	58 (4.3%)	7 (6.2%)	
Other/Unknown	189 (51.5%)	318 (41.2%)	1,734 (38.9%)	2,328 (40.2%)	639 (47.6%)	59 (52.2%)	

Bold indicates significant p value (p < 0.05).

¹Chi² test.

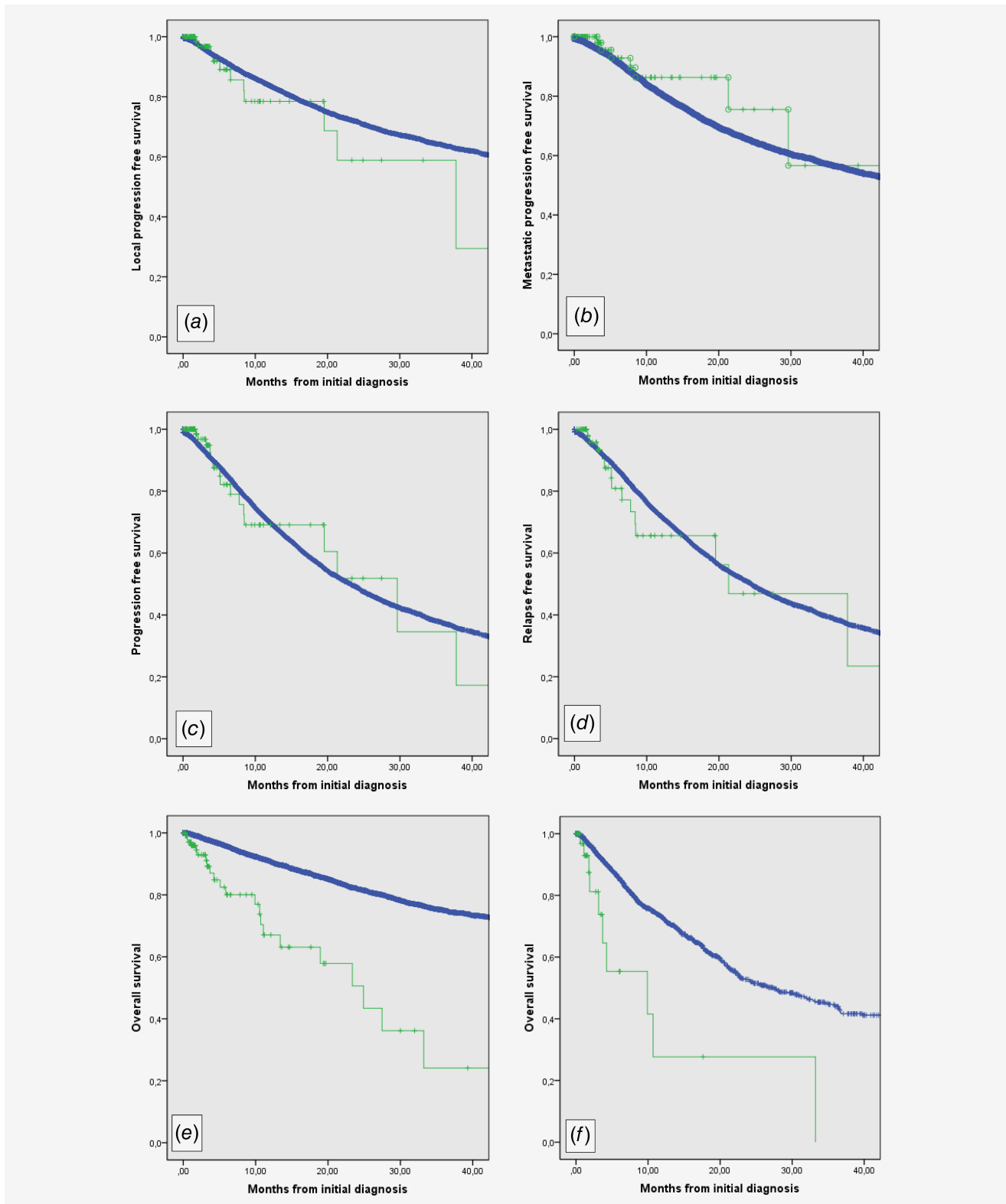


Figure 1. Progression, relapse and survival in sarcoma patients aged over or under 90. (a) Local progression-free survival of patients aged over 90 (green) and younger (blue). (b) Metastatic progression-free survival of patients aged over 90 (green) and younger (blue). (c) Progression-free survival of patients aged over 90 (green) and younger (blue). (d) Relapse-free survival of operated patients aged over 90 (green) and younger (blue). (e) Overall survival of patients aged over 90 (green) and younger (blue). (f) Overall survival of nonoperated patients aged over 90 (green) and younger (blue). [Color figure can be viewed at wileyonlinelibrary.com]

must be compared to the 50 months life expectancy for the general French population at the age of 90.¹⁴

To the best of our knowledge, this is the first series reporting on the different biology and natural history of patients with sarcomas occurring at a very high age. Sarcoma occurring after 90 has a specific biology and natural history, but not intrinsically a worse cancer-specific prognosis. If fit according to geriatric

assessment, this patient population, should be treated according to the general CPGs for sarcomas. It is reasonable to infer a similar statement for younger geriatric sarcoma patients.

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