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ORIGINAL ARTICLE

Surgery in reference centers improves survival of sarcoma patients: a nationwide study

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Background: NETSARC (netsarc.org) is a network of 26 sarcoma reference centers with specialized multidisciplinary tumor boards (MDTB) aiming to improve the outcome of sarcoma patients. Since 2010, presentation to an MDTB and expert pathological review are mandatory for sarcoma patients nationwide. In the present work, the impact of surgery in a reference center on the survival of sarcoma patients investigated using this national NETSARC registry.

Patients and methods: Patients' characteristics and follow-up are prospectively collected and data monitored. Descriptive, uni- and multivariate analysis of prognostic factors were conducted in the entire series ($N = 35\,784$) and in the subgroup of incident patient population ($N = 29\,497$).

Results: Among the 35 784 patients, 155 different histological subtypes were reported. 4310 (11.6%) patients were metastatic at diagnosis. Previous cancer, previous radiotherapy, neurofibromatosis type 1 (NF1), and Li–Fraumeni syndrome were reported in 12.5%, 3.6%, 0.7%, and 0.1% of patients respectively. Among the 29 497 incident patients, 25 851 (87.6%) patients had surgical removal of the sarcoma, including 9949 (33.7%) operated in a NETSARC center. Location, grade, age, size, depth, histotypes, gender, NF1, and surgery outside a NETSARC center all correlated to overall survival (OS), local relapse free survival (LRFS), and

event-free survival (EFS) in the incident patient population. NF1 history was one of the strongest adverse prognostic factors for LRFS, EFS, and OS. Presentation to an MDTB was associated with an improved LRFS and EFS, but was an adverse prognostic factor for OS if surgery was not carried out in a reference center. In multivariate analysis, surgery in a NETSARC center was positively correlated with LRFS, EFS, and OS [$P < 0.001$ for all, with a hazard ratio of 0.681 (95% CI 0.618–0.749) for OS].

Conclusion: This nationwide registry of sarcoma patients shows that surgical treatment in a reference center reduces the risk of relapse and death.

Key words: sarcoma, resection, surgery, relapse, survival, reference center

Introduction

Sarcomas are a heterogeneous group of rare connective tissue cancers, with variable clinical presentations, and an estimated incidence close to 6.2/100 000/year [1–4]. In all clinical practice guidelines, it is recommended that the management of sarcoma patients should be carried out by a dedicated multidisciplinary team, including expert pathologists and surgeons, treating a large number of patients [5–7]. Because of their rarity, sarcoma is often initially misrecognized, misdiagnosed, and as a consequence not treated according to clinical practice guidelines [5–9]. Inadequate diagnostic procedure and treatment, e.g. enucleation of the tumor as initial surgery without initial imaging or biopsy, are observed in a large fraction of patients and often qualified as 'whoops' procedures [10–12]. We recently reported that presentation to a specialized multidisciplinary tumor board (MDTB) was independently correlated to reduction in the risk of relapse in a nationwide study involving the NETSARC Network [12]. Similar observations were reported by several other national initiatives [13–15].

Optimal surgical removal of sarcoma, with *en bloc* macroscopic resection and histological clear margins is the mainstay of the curative treatment of localized soft tissue sarcoma (STS) [5–9]. This quality of initial surgery is a major prognostic factor for recurrence-free survival and overall survival (OS) in all series [16–21].

In most European (and actually worldwide) countries, including France, the treatment of patients with sarcoma can be carried out primary care oncology hospital or clinic, with no specific guidance on the nature of the required multidisciplinary team or on number of patients treated. Conversely in Scandinavian countries as well as in the UK the management of sarcoma patients must be carried out in dedicated reference centers [9, 22]. It is also recommended that patients with a suspected diagnosis of sarcoma should be referred at a sarcoma center before any treatment in international Clinical Practice Guidelines [5–8].

The French National Cancer Institute (INCa) funded a clinical network for sarcoma (called NETSARC) in 2009, to improve the management and outcome of sarcoma patients. Twenty-six reference centers throughout the nation were identified. A Network for expert pathology diagnosis in sarcoma (RRePS) gathering 23 reference centers for pathology in charge of the second histological review for each suspected case was also created. A common database (netsarc.org) gathering all cases of sarcoma presented to MDTB was created and implemented, collected data on the diagnostic, therapeutic management, and the clinical outcome in terms of relapse and survival.

From 1 January 2010 to 1 May 2018, this database prospectively included a 47 023 patient population with 35 784 patients with sarcoma or tumor of intermediate malignancy. 11 239 (24%) patients in the database discussed in a NETSARC MDTB had a diagnosis which was not that of a sarcoma (benign tumor, e.g. lipoma, carcinoma, lymphoma, etc.).

The aim of the present study was to evaluate (i) the impact of predisposing conditions and patient history and (ii) the impact of surgery carried out in a NETSARC reference center on relapse and survival in the population of patients included in the NETSARC database.

Patients and methods

The network

Each NETSARC center organizes an MDTB gathering sarcoma specialized pathologist(s), radiologist(s), surgeon(s), radiation oncologist(s), medical oncologist(s), and often molecular biologist(s), orthopedist(s), and pediatrician(s). All sarcoma or suspected sarcoma patient cases presented to the MDTB of all 26 centers were recorded in the database, by a dedicated team of Clinical research assistant, supervised by three coordinating centers (Centre Leon Bérard, Gustave Roussy, Institut Bergonié). Patient files may be presented before any diagnostic procedure, before initial biopsy, before primary surgery, after primary surgery, at relapse, and/or in case of a possible inclusion in a clinical trial. Patients and treatment data were prospectively included and regularly updated by the dedicated study coordinators. A monitoring of the centers activity is carried out by the three coordinating centers on a regular basis. The contribution of the different centers is presented in supplementary Table S1 (available at *Annals of Oncology* online).

The NETSARC database

The NETSARC database allows (i) to exhaustively describe the incident and prevalent population of sarcoma patients in France, by cross comparison of the pathological review database (rreps.org) and of the clinical database (netsarc.org), (ii) to monitor the diagnostic and initial treatment procedures, and (iii) to monitor patient outcome in particular survival and relapse. The database includes a limited set of data, on purpose, describing patients and tumor characteristics, surgery, relapse, and survival [12]. The center which carried out the first resection is documented, as well as potential secondary surgery, and the final quality of resection after all surgical procedures. The surgical resection system (R) from the Union Internationale contre le Cancer was chosen to define the quality of surgery, including the margins of resection. This system defines the quality of resection (R) using the surgical and pathological report: R0 = macroscopically complete resection with an absence of tumor cells in the resection margins, R1 = same, but with tumor cells visible on resection margins, and R2 = macroscopic residual disease.

Of note, 11 239 (24%) out of the 47 023 patients in the database discussed in a NETSARC MDTB had a diagnosis which was not that of a sarcoma (benign tumor, e.g. lipoma, carcinoma, lymphoma, etc.). The case was presented for discussion after the pathology review for further discussion, or before the pathology review (which was then conducted

afterward at the request of the MDTB). It is important to note that in NETSARC, patients with sarcoma or suspected sarcoma can enter the process of MDTB either through the pathology network, or directly by the physician, leading in both cases to a final MDTB review after central pathology confirmation. All data presented here were extracted from the NETSARC.org database accessible online.

Statistical analyses

The categorical data were summarized by the frequencies and percentages, and the continuous covariates have been summarized with median, range, and numbers of observations. The statistical test used for comparison was a chi-square test (or a Fisher's exact test) for categorical covariates, without adjustment for multiple comparisons. The diagnostic date is the date of histological diagnosis (biopsy or first surgery). Survival is calculated from the date of diagnosis to the date of last follow-up or death. Local relapse free survival (LRFS) is computed from the diagnostic date to the date of the last follow-up or the date of the first local recurrence. Event-free survival (EFS) was computed from the date of diagnosis to the date of the last follow-up or the date of the first local relapse, metastasis progression or death, whichever comes first.

Survival curves were plotted using a Kaplan–Meier method. Survival was compared using the log-rank test. Univariate and multivariate analysis for LRFS, EFS, and OS included (i) classical prognostic factors for sarcoma [age, gender, grade, size, site, metastasis at diagnosis, histotypes—in particular the most frequent histotypes leiomyosarcoma (LMS), LPS, undifferentiated pleomorphic sarcoma (UPS), gastrointestinal stromal tumor (GIST), etc.] and (ii) also preexisting conditions which are collected routinely in the NETSARC database [previous cancer, neurofibromatosis type 1 (NF1), p53, previous radiotherapy (RT)] [18]. It also included prognostic factors identified in univariate analysis, e.g. presentation to a NETSARC MDTB before versus after first treatment, primary and/or secondary surgery in a NETSARC center. Cox proportional hazards model was used for the multivariate analysis, introducing parameters significant ($P < 0.05$) in univariate analysis. Factors included in the multivariate model were identified by a backward selection procedure which entails including all the covariates in the model and removing those, whose P-value is higher than 0.10, one at a time. At each step of the model, all included variables were tested and removed if they were no longer associated with the outcome considering a 5% type I error (P-value ≥ 0.05). All statistical tests were two-sided. All statistical analyses were carried out using SPSS (version 22.0).

Results

Patient population

Between 1 January 2010 and 1 May 2018, 35 784 patients with sarcoma or mesenchymal tumors of intermediate malignancy were prospectively included in the NETSARC database. 29 467 (82.4%) patients were diagnosed from 1 January 2010 onward (designated as the incident population) and 6287 patients were diagnosed before, but presented to a NETSARC MDTB after 1 January 2010. The patient population studied here is that of all patients included in the database, of any age, with a histologically reviewed and confirmed soft tissue or visceral sarcoma, GIST, bone sarcomas, or tumor of intermediate malignancy in any anatomic site. Patient characteristics are presented in Table 1.

Characteristics of patients operated in NETSARC centers

Among the 29 497 incident patients, 9954 (33.7%) had a first surgery in a NETSARC center, 15 896 (54.8%) had been operated outside of a NETSARC center, 3647 (12.4%) had not been resected at last follow-up. Among those operated, the proportion operated in a NETSARC center increased from 30.4% to 42.9% from 2010 to 2017 ($P < 0.001$). 14 509 (49.2%) patients of the incident population were presented to a NETSARC MDTB before first treatment (Table 1), the proportion increased from 33.3% to 56.2% between 2010 and 2017.

We analyzed the characteristics of patients operated in NETSARC in the incident group ($N = 29\,497$, since January 2010) (Table 1). Overall, the characteristics of patients operated in a NETSARC center were less favorable, with a higher proportion of patients with large tumors ($P < 0.001$), grade 3, retroperitoneal, UPS histology and a lower proportion of patients with tumors of intermediate malignancy (all $P < 0.001$). A lower proportion of sarcoma from uterus, head and neck, or internal trunk, GIST, desmoid tumors, and tumors of intermediate malignancy was observed in patients operated in NETSARC centers (Table 1).

More patients operated in NETSARC had been presented to a NETSARC MDTB (64.0% versus 41.7%, $P < 0.001$) before surgery, as expected. Biopsy (core or incisional) before surgery were carried out in 8585 of 15 897 (54.0%) patients operated outside NETSARC versus 8096 of 9954 (81.3%) of patients operated in NETSARC ($P < 0.001$). Adequate imaging before surgery had been carried out in 9378 (59.0%) versus 8239 (82.8%) of patients operated outside versus within NETSARC ($P < 0.001$).

Table 2 describes the predisposing conditions reported for the 35 784 patients, the number of different histological subtypes associated with these conditions. Previous cancer, previous RT, a diagnosis of NF1, and immune-depression were the most frequent predisposing condition. All others were observed in $\leq 0.1\%$ of patients. Preexisting conditions were generally associated with specific predominant histological subtypes, consistently with the literature (Table 2) [1].

A previous diagnosis of cancer (12.7% versus 11.58, $P = 0.03$), sarcoma in an irradiated field (4.0% versus 3.0%, $P < 0.001$), history of Ollier's disease (0.2% versus 0.1%, $P = 0.003$), and multiple exostoses (0.2% versus <0.1%, $P < 0.001$) were more frequently reported in patients operated in NETSARC centers. Conversely, a history of Gardner's disease (<0.1% versus 0.1%, $P = 0.02$), retinoblastoma (<0.1% versus 0.1%, $P = 0.02$), and immunodepression (0.2% versus 0.4%, $P = 0.04$) were less frequently reported in patients operated in NETSARC centers reflecting probably referral patterns from organ specialists. A history of NF1 and of a Li–Fraumeni syndrome was observed at similar levels in the two groups of patients.

Quality of surgery

The quality of the surgery of operated patients was then compared between the two groups including only the 25 851 [patients who had been operated of their primary tumor (87.6% of the incident patient population]. Table 3 presents the rate of R0, R1, and R2 resection in NETSARC and non-NETSARC centers, at initial surgery, and after final surgery: the R0 rate in NETSARC centers was over twofold that of non-NETSARC centers, while the proportion of R2 and R unknown surgery was over twofold higher in non-NETSARC centers (Table 3, $P < 0.001$). The rate of reoperation was also over twofold superior in non-NETSARC centers (Table 3). Figure 1A–C presents LRFS, EFS, and OS according to the R status in all 25 851 operated

Table 1. Description of the population of 35 784 patients with connective tissue tumors in Netsarc

Characteristics	Total (*N* = 35 784)	Populations *N* (%) incident	Operated in NETSARC (*N* = 9954)	*P*[a]
Gender				
Male	17 577 (49.1%)	14 661 (49.5%)	4983 (50.1%)	
Female	18 207 (50.9%)	14 886 (50.5%)	4971 (49.9%)	0.19
Age at first diagnosis				
Mean (min–max)	60.8 (0–106)	55.3 (0–106)	53.8 (0–99)	0.000
<18	1622 (4.5%)	1359 (4.6%)	522(5.2%)	
18–40	7019 (19.6%)	5682 (19.3%)	2009 (20.2%)	
41–60	10 993 (30.7%)	8763 (29.7%)	3056 (30.7%)	
61–80	12 599 (35.2%)	11 070 (37.5%)	3711 (37.3%)	
>80	2736 (7.6%)	2622 (8.9%)	656 (6.6%)	
Missing	815 (2.3%)	1 (0.0%)	0	0.000
Size of the tumor (mm)				
Available in *N* = 11 894 (33.2%)				
Median (min–max)	91 (1–900)	89.6 (1–900)	97.7 (1–600)	0.000
Primary site				
Soft tissue	22 971 (64.2%)	19 288 (65.4%)	6398 (64.3%)	
Visceral		5681 (19.3%)	1404 (14.1%)	
Bone	5447 (15.2%)	4528 (15.4%)	2152 (21.6%)	0.000
Depth				
Deep seated	23 244 (64.9%)	19 490 (64.3%)	6592 (66.2%)	
Superficial	7007 (19.6%)	6043 (20.5%)	1724 (17.3%)	
Not reported	5533 (15.5%)	4494 (15.2%)	1638 (16.5%)	0.000
Category				
Sarcoma	29 500 (82.4%)	24 148 (81.9%)	8346 (83.8%)	
Intermediate malignancy	6284 (17.6%)	5349 (18.1%)	1608(16.2%)	0.000
Histological subtype (11 most frequent)				
Leiomyosarcoma	4182 (11.7%)	3396 (11.5%)	837 (8.4%)	
UPS	3867 (10.8%)	3495 (11.8%)	1253 (12.6%)	
GIST	2690 (7.3%)	2112 (7.2%)	637 (6.4%)	
DDLPS	2277(6.4%)	2114 (7.2%)	777 (7.8%)	
WDLPS	2110 (5.9%)	1714 (5.8%)	842 (8.5%)	
Desmoid	1814 (5.1%)	1603 (5.4%)	205 (2.1%)	
Myxofibrosarcoma	1170 (3.3%)	995 (3.4%)	362 (3.6%)	
Chondrosarcoma	1136 (3.2%)	901 (3.1%)	454 (4.6%)	
Ewing	1136 (3.2%)	946 (3.2%)	360 (3.6%)	
Angiosarcoma	1117 (3.1%)	985 (3.3%)	278 (2.8%)	
Synovial	966 (2.7%)	741 (2.5%)	192 (2.9%)	0.000
Others (144 histotypes, *N* range 1–904)	13 319 (37.4%)	10 495 (35.6%)	3757 (37.7%)	
Grade				
1	3965 (11.1%)	3058 (10.4%)	1370 (13.8%)	0.000
2	6165 (17.2%)	5053 (17.1%)	1910 (19.2%)	0.000
3	7616 (21.3%)	6509 (22.1%)	2559 (25.7%)	0.000
Unknown	10 163 (28.4%)	8576 (29.1%)	2309 (23.2%)	0.000
Non-applicable	7875 (22.2%)	6301 (21.4%)	1806 (18.1%)	0.000
Site of the primary tumor				
Lower limb	9342 (26.1%)	7805 (26.5%)	3693 (37.1%)	0.000
Thigh	4636 (13%)	3872 (13.1%)	1935 (19.4%)	0.000
Upper limb	3487 (9.7%)	2861 (9.7%)	977 (9.8%)	0.631
Trunk wall	5506 (15.4%)	4783 (16.2%)	1535 (15.4%)	0.008
Retroperitoneum	2945 (8.2%)	2278 (7.7%)	915 (9.2%)	0.000
Gastrointestinal	2890 (8.1%)	2417 (8.2%)	679 (6.8%)	0.000
Uterus	1733 (4.8%)	1357 (4.6%)	224 (2.3%)	0.000
Head and neck	2162 (6.0%)	1774 (6.0%)	341 (3.4%)	0.000
Other	7719 (21.6%)	6622 (21.1%)	1610 (16.1%)	0.000
Metastases at diagnosis				
No	27 952 (78.1%)	23 006 (78.0%)	8566 (86.1%)	

Continued

Table 1. *Continued*

Characteristics	Total (*N* = 35 784)	Populations *N* (%) incident	Operated in NETSARC (*N* = 9954)	*P*[a]
Yes	4180 (11.6%)	3603 (12.2%)	701 (7.1%)	
Unknown	3652 (10.2%)	2888 (9.8%)	687 (6.9%)	0.000
N pts operated	31 863 (89.0%)	25 851 (87.6%)	9954 (100%)	
Patients presented to NETSARC MDTB before treatment	NA	14 509 (49.2%)	6372 (64.0%)	0.000

[a]*P*-value comparing patients operated outside versus inside NETSARC centers.
DDLPS, dedifferentiated liposarcoma; GIST, gastrointestinal stromal tumor; NA, Not applicable; UPS, undifferentiated pleomorphic sarcoma; WDLPS, well differentiated liposarcoma.

Table 2. History of previous cancer or cancer predisposition

	N (%)	Number of different histotypes (total *N* = 155)	Predominant histotype	*N* (%)
History				
None	20 540 (57.4)	153 (98.7)	LMS	2327 (11.3)
Unknown	7098 (19.8)	137 (88.4)	LMS	868 (12.2)
Previous cancer	4577 (12.2)	119 (76.8)	UPS	690 (15.1)
In irradiated field	1125 (3.1)	89 (57)	Angiosarcoma	376 (30.7)
NF1	288 (0.8)	25 (16)	MPNST	186 (64.6)
			GIST	50 (17.7)
Immunodepression	139 (0.4)	37(23.8)	Kaposi	64 (46.0)
Gardner	51 (0.1)	1 (0.6)	Desmoids	51 (100)
Multiple exostoses	43 (0.1)	3 (0.6)	Chondrosarcoma	38 (88.4)
Ollier	39 (0.1)	8 (5.1)	Chondrosarcoma	33 (81.2)
Li–Fraumeni	37 (0.1)	23 (14.8)	LMS	8 (21.6)
Paget disease of bone	20 (0.1)	13 (8.3)	Osteosarcoma	5 (25)
Retinoblastoma	16 (0.04)	9 (5.8)	LMS	6 (37)
Rothmund–Thomson	2 (0.005)	1	Osteosarcoma	
Maffucci syndrome	2 (0.005)	1	Chondrosarcoma	
NF2	1 (0.003)	1	GIST	
Werner syndrome	1 (0.003	1	LPS	
Stratiakis-Carney	1 (0.003)	1	GIST	
Other[a]	2773 (7.7)	124 (80.0)	LMS	311 (11.2)

[a]No details are provided in the database.
GIST, gastrointestinal stromal tumor; LMS, leiomyosarcoma; NF1, neurofibromatosis type 1; UPS, undifferentiated pleomorphic sarcoma.

Table 3. Quality of resection in patients operated within or outside NetSARC

	First surgery outside NETSARC or no data (*N* = 15 897), *n* (%)	First surgery in NetSARC (*N* = 9954), *n* (%)	*P*
Initial			
R0	3113 (19.6)	5280 (53.0)	
R1	3208 (20.2)	2388 (24.0)	
R2	1659 (8.5)	417 (4.2)	
Unknown	7917 (50.0)	1869 (18.8)	**<0.000**
Reoperation	2498 (15.7)	616 (6.2)	**<0.000**
Final			
R0	4693 (29.5)	5643 (56.7)	
R1	2492 (15.7)	2170 (21.8)	
R2	981 (6.2)	302 (3.0)	
Unknown	7731 (48.6)	1839 (18.5)	**<0.000**

The bold characters are used when the *P* value is significant.

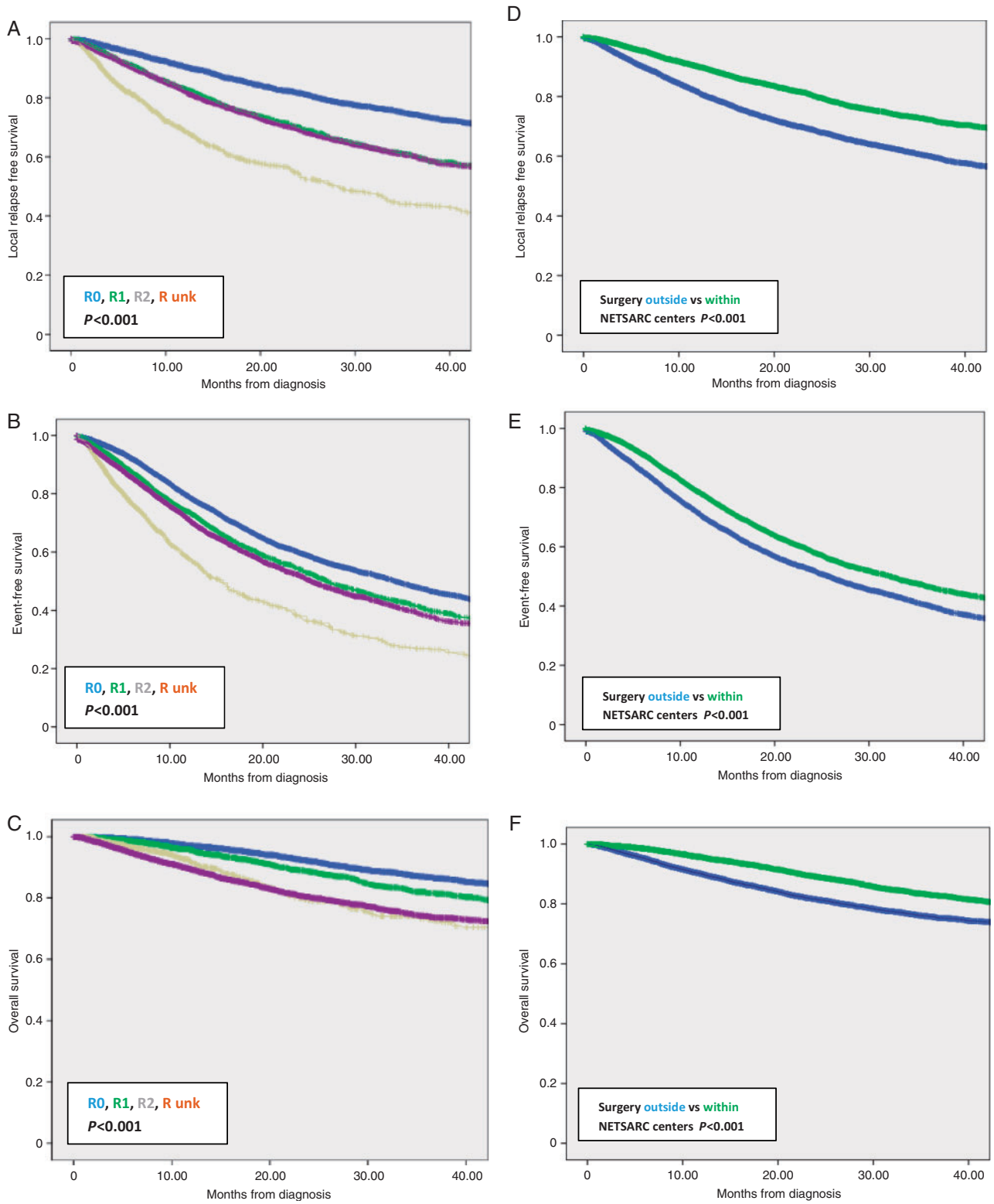

Figure 1. Relapse and survival of the incident population of 29 497 patients. (A, B, C) Local relapse free survival (LRFS), event-free survival (EFS) and overall survival (OS) of patients with a final R0, R1, R2 and R unknown resection. (D, E, F) LRFS, EFS and OS of patients operated with a NETSARC center or outside a NETSARC center.

incident patients. The absence of a documented R was associated with a higher risk of relapse and death: the R2 and R unknown groups had a similar OS indicating that the lack of information is by itself a negative predictive marker (Figure 1).

Survival

Prognostic factors for relapse and death were then evaluated in the incident population of 25 851 operated patients. Table 4

Table 4. Prognostic factors for local relapse free (LRFS), event-free (EFS) and overall survival (OS) in the operated incident patient population (N = 25 851)

	LRFS		EFS		OS	
	HR	P	HR	P	HR	P
Parameter						
Male gender	1.015	0.649	**1.098**	**0.045**	**1.213**	**0.000**
Age	**1.010**	**0.000**	**1.008**	**0.000**	**1.015**	**0.000**
Bone	0.999	0.986	0.881	0.068	**1.435**	**0.000**
Visceral	1.097	0.058	1.050	0.588	**1.878**	**0.002**
Deep seated	0.943	0.097	1.050	0.431	**1.488**	**0.000**
Tumor size	**1.002**	**0.000**	**1.002**	**0.000**	**1.003**	**0.000**
Histological subtype						
Leiomyosarcoma	**0.690**	**0.000**	**1.129**	**0.082**	**0.700**	**0.000**
UPS	1.075	0.145	0.940	0.397	**1.201**	**0.003**
GIST	**0.267**	**0.000**	**0.254**	**0.000**	**0.158**	**0.000**
DDLPS	**1.271**	**0.000**	**0.789**	**0.019**	**0.830**	**0.016**
WDLPS	**0.633**	**0.000**	**0.516**	**0.000**	**0.197**	**0.000**
Desmoid	**1.490**	**0.000**	1.079	0.630	**0.227**	**0.000**
Intermediate malignancy	0.965	0.462	**0.520**	**0.000**	**0.122**	**0.000**
Grade						
1	**0.716**	**0.000**	**0.635**	**0.000**	**0.347**	**0.000**
2	1.074	0.100	1.013	0.854	1.020	0.754
3	**1.335**	**0.000**	**1.540**	**0.000**	**2.091**	**0.000**
Site						
Lower limb	**1.015**	**0.766**	**0.843**	**0.035**	**0.760**	**0.000**
Upper limb	**1.376**	**0.000**	0.892	0.252	**0.692**	**0.000**
Trunk wall	**1.369**	**0.000**	1.025	0.777	1.045	0.541
Uterus	**1.245**	**0, 005**	1.230	0.071	**1.672**	**0.000**
Retroperitoneal sarcoma	**1.773**	**0.000**	**1.364**	**0.004**	**1.262**	**0.006**
Other internal trunk	**1.374**	**0.000**	1.068	0.511	**1.532**	**0.000**
HN	**1.645**	**0.000**	1.122	0.336	1.009	0.930
Metastasis at diagnosis	1.004	0.946	**3.082**	**0.000**	**3.834**	**0.000**
Preexisting conditions						
Previous cancer	**1.129**	**0.013**	1.016	0.815	**1.193**	**0.007**
Previous RT	**1.557**	**0.000**	1.020	0.334	**1.763**	**0.000**
NF1	**1.393**	**0.027**	**1.524**	**0.035**	**2.072**	**0.000**
P53	0.652	0.340	1.868	0.168	0.292	0.219
Immunodepression	0.978	0.940	1.149	0.716	0.629	0.300
Rb	1.761	0.258	1.005	0.995	0.919	0.932
Gardner	1.691	0.165	1.894	0.278	0.404	0.365
Ollier	0.785	0.588	2.222	0.262	0.739	0.675
Multiple exostose	1.004	0.946	0.632	0.647	0.000	0.339

The bold characters are used when the *P* value is significant.
DDLPS, dedifferentiated liposarcoma; GIST, gastrointestinal stromal tumor; HR, hazard ratio; NF1, neurofibromatosis type 1; UPS, undifferentiated pleomorphic sarcoma; WDLPS, well differentiated liposarcoma.

presents the prognostic factors for LRFS, EFS, and OS, with a median follow-up of 17 months. Grade, tumor site, histotype, tumor size, and age were correlated to OS, EFS, and local relapse (Table 4). Previous cancer, previous RT, and NF1 diagnosis also correlated negatively to event-free and OS. No other genetic predisposition influenced LRFS, EFS, or OS in this series.

Table 5. Multivariate analysis of prognostic factors for relapse and survival in the incident population of operated patients

	Hazard ratio (95% CI)		*P*-value
Local relapse free survival			
NF1	1.748	(1.297–2.354)	0.000
Desmoid tumor	1.670	(1.420–1.965)	0.000
Previous RT	1.532	(1.335–1.756)	0.000
Retroperitoneal sarcoma	1.362	(1.213–1.529)	0.000
Bone	1.290	(1.167–1.425)	0.000
Grade 3	1.181	(1.098–1.269)	0.000
DDLPS	1.157	(1.029–1.302)	0.016
Head and neck sarcoma	1.124	(0.988–1.279)	0.075
UPS	1.100	(0.995–1.215)	0.063
Age at diagnosis	1.008	(1.006–1.010)	0.000
Deep	0.930	(0.866–0.998)	0.041
Lower limb	0.872	(0.808–0.941)	0.001
Intermediate malignancy	0.820	(0.734–0.915)	0.000
Grade 1	0.689	(0.615–0.772)	0.000
NETSARC MDT before treatment	0.670	(0.623–0.720)	0.000
Surgery in a NETSARC center	**0.654**	**(0.610–0.702**)	0.000
LMS	0.650	(0.585–0.723)	0.000
GIST	0.279	(0.229–0.341)	0.000
Disease-free survival			
Metastases at diagnosis	1.766	(1.646–1.896)	0.000
NF1	1.537	(1.222–1.933)	0.000
Size ≥100 mm	1.431	(1.328–1.541)	0.000
Grade 3	1.392	(1.319–1.467)	0.000
Uterine sarcoma	1.300	(1.162–1.453)	0.000
Retroperitoneal sarcoma	1.260	(1.136–1.398)	0.000
Desmoid tumor	1.219	(1.048–1.418)	0.010
Previous RT	1.195	(1.064–1.341)	0.003
Bone	1.169	(1.085–1.259)	0.000
UPS	1.095	(1.019–1.178)	0.015
Gender	1.094	(1.042–1.149)	0.000
Visceral	1.083	(0.988–1.188)	0.093
Age at diagnosis	1.007	(1.005–1.009)	0.000
Trunk wall	0.893	(0.821–0.972)	0.009
Upper limb	0.890	(0.807–0.981)	0.019
Lower limb	0.874	(0.808–0.945)	0.001
Head and neck sarcoma	0.873	(0.773–0.986)	0.028
DDLPS	0.857	(0.779–0.944)	0.002
Surgery in a NETSARC center	**0.843**	**(0.799–0.889**)	0.000
NETSARC MDT before treatment	0.800	(0.758–0.843)	0.000
WDLPS	0.653	(0.561–0.761)	0.000
Intermediate malignancy	0.649	(0.590–0.715)	0.000
Grade 1	0.590	(0.534–0.652)	0.000
GIST	0.324	(0.281–0.373)	0.000
Overall survival			
Metastases at diagnosis	3.153	(2.852–3.483)	0.000
NF1	2.467	(1.761–3.456)	0.000
Size ≥100 mm	1.981	(1.760–2.227)	0.000
NETSARC MDT before treatment	1.563	(1.423–1.718)	0.000
Grade 3	1.511	(1.381–1.654)	0.000
Previous RT	1.335	(1.113–1.602)	0.002
Visceral	1.333	(1.156–1.539)	0.000
Bone	1.278	(1.112–1.468)	0.001
Uterine sarcoma	1.246	(1.034–1.501)	0.021
Deep	1.229	(1.108–1.363)	0.000

Continued

Table 5. *Continued*

	Hazard ratio (95% CI)		*P*-value
Gender	1.189	(1.086–1.301)	0.000
UPS	1.133	(1.002–1.282)	0.048
Age at diagnosis	1.017	(1.015–1.019)	0.000
Trunk wall	0.832	(0.728–0.951)	0.007
DDLPS	0.782	(0.667–0.916)	0.003
Surgery in a NETSARC center	**0.681**	**(0.618–0.749)**	**0.000**
Lower limb	0.663	(0.585–0.752)	0.000
Upper limb	0.621	(0.519–0.742)	0.000
LMS	0.615	(0.537–0.704)	0.000
Grade 1	0.431	(0.342–0.544)	0.000
WDLPS	0.385	(0.245–0.605)	0.000
GIST	0.154	(0.117–0.203)	0.000
Intermediate malignancy	0.154	(0.112–0.212)	0.000

The bold characters are used when the *P* value is significant.
DDLPS, dedifferentiated liposarcoma; GIST, gastrointestinal stromal tumor; HR, hazard ratio; LMS, leiomyosarcoma; NF1, neurofibromatosis type 1; UPS, undifferentiated pleomorphic sarcoma; WDLPS, well differentiated liposarcoma.

Presentation of patients to an MDTB before initial treatment, and surgery in a NETSARC center correlated to a better LRFS, EFS, while OS was worse in this subgroup (not shown). Importantly, initial surgery in a NETSARC center was associated with a significantly improved EFS and OS (Figure 1D–F). This was observed regardless of the number of patients operated in individual NETSARC center (not shown). The OS of patients presented to a NETSARC MDTB and operated outside of NETSARC center was particularly poor (supplementary Figure S1, available at *Annals of Oncology* online).

In multivariate analysis, LRFS, EFS, and OS were influenced by patient related factors (gender, age), tumor presentation (site, size, location, metastases at diagnosis), histotypes, and grade. In addition, previous RT negatively correlated to LRFS. Importantly, NF1 condition was the strongest negative prognostic factor for LRFS, EFS, and OS (Table 5). Surgery in a NETSARC center was found consistently associated with a reduction in the risk of local relapse, progression, and death, with hazard ratio of 0.64, 0.83, and 0.68 for LRFS, EFS, and OS (Table 5). The favorable prognostic value of surgery in a NETSARC center was retained in addition to the presentation to a NETSARC MDTB. The later also remain an independent prognostic factor associated with a reduction in the risk of local relapse and EFS, but not OS (Table 5).

When the analysis was conducted in the same incident population of sarcoma, excluding patients with metastatic disease at diagnosis ($N = 23\,327$), surgery in a NETSARC center remained an independent prognostic factor for LRFS, EFS, and OS (not shown). Similarly, this analysis was conducted in the entire population of 35 784 patients, pooling incident patients ($N = 29497$), and patients diagnosed before 1 January 2010 ($N = 6287$). The latter group is of course biased with an over representation of longer survivors and of relapsing patients given the mode of entry of a presentation to an MDTB. Surgery in a NETSARC center was retained as independent favorable prognostic factors for LRFS, EFS, and OS in this exhaustive series (not shown).

Discussion

In the present work, we investigated the impact of surgery in a reference center for sarcoma on relapse and survival in a nationwide series of 35 784 sarcoma patients seen in NETSARC MDTB since 2010. We focused on the population of incident patients diagnosed from 1 January 2010. We also analyzed the incidence and prognostic impact of preexisting conditions.

Clinical practice guidelines recommend a multidisciplinary management by reference centers for rare cancers, in particular for sarcoma [5–9]. Management in large volume centers and in network of reference centers improves adhesion to clinical practice guidelines [12–17].

The NETSARC network aims at improving the management of sarcoma patients and their outcome nationwide. NETSARC prospectively collected all sarcoma cases reviewed in one of the 26 MDTB of the network since 1 January 2010. Centralized expert pathology review by the RREPS network is mandatory nationwide since 1 January 2010, ensuring that the diagnosis of sarcoma reported in this database is accurate. It took 3 years for NETSARC to accrue each year the number of expected incident patients. Since 2013, the number of new cases of sarcomas included in the database reached the expected incidence of these diseases in this country of 67 million inhabitants, with a 6.2/100 000/year incidence [2–4]. These numbers strongly suggest that this database gathers a close to exhaustive nationwide cohort of sarcoma patients.

In this work, we focused the survival analysis on the 29 497 incident patients with sarcoma with an initial diagnosis from 1 January 2010 to 1 May 2018. The analysis of this prospective nationwide cohort of patients indicates that the survival of sarcoma patients is improved when they are operated in a reference center. When surgery is not carried out in a reference center ($N = 15\,897$), the rate of R0 resections is 50% lower to that of patients operated in a NETSARC center, while conversely the rate of R2 resection is more than doubled. Reoperations are carried out 2.5-fold more often in patients firstly not operated in a NETSARC center. Finally, the quality of the final surgical intervention of patients operated upfront outside NETSARC center, as evaluated by the rate of R0, R1, R2, and unknown resection, was significantly inferior even after a secondary surgery: with a lower rate of R0 resection and a higher rate of R2 resection. Importantly, this documentation of the quality of surgery was missing in a significantly higher proportion for surgeries carried out outside a NETSARC center versus NETSARC center. The lack of documentation of the R status is by itself a negative prognostic factor. When the primary surgery was done outside a NETSARC center, a secondary surgery in a NETSARC center did not allow to compensate the initial low rate of R0 surgery: the rate of inadequate surgery (R2, R unknown) surgery as final surgery remain significantly increased in the population of patients which was not initially operated in a NETSARC center.

As expected, reoperations were more frequent in patients operated outside NETSARC. We previously reported that this was an important component of the increased cost of the patient pathways for patients operated outside NETSARC [23, 24]. This study estimated a €4000 net increase of the cost of the overall procedure per patient managed outside guidelines, and it is noteworthy that over 50% of the 29 497 patients had either no previous biopsy, no

adequate imaging, or were operated outside NETSARC. Not only these patients had a higher relapse rate and worse survival, but the excess cost of their suboptimal treatment may be estimated to 60 million euros over the study period [25, 26].

Patients operated in a NETSARC center had significantly worse prognostic characteristics as compared with those operated outside NETSARC, with larger tumors of higher grade and unfavorable locations (retroperitoneal) and histological subtypes; however, the differences in the two groups probably also reflected referral patterns of organ specialists, with a lower proportion of sarcoma from uterus, head and neck, or GIST in NETSARC centers, as well as less immunosuppressed patients and Gardner syndromes. These differences also reflected practices: for desmoid tumors, where the strategy of watchful waiting has been proposed in reference centers since a decade [27, 28], the proportion of operated patients was very low in NETSARC centers. Surgery in a NETSARC center is an independent prognostic factor for LRFS, EFS, and OS. The reduction of the risk of relapse and death is close to 35% indicating that centralization of surgery is probably the most efficient, and actually cost saving strategy to improve survival and reduce the risk of relapse and death of sarcoma patients in localized phase. Indeed, no other treatment procedure or medication is reported to enable such an increase survival of sarcoma patients to this extent, in view of the current scientific literature.

The improvement in survival observed when surgery is carried out in a NETSARC center comes in addition to the presentation to a NETSARC MDTB in the multivariate model. We had previously reported in the series of the first 12 528 patients that the presentation of the patient to an MDTB before any treatment procedure is associated with a better compliance to the clinical practice guidelines, a better quality of surgery, a better relapse free survival [12]. This later parameter is indeed associated with a better LRFS and EFS as previously described [12], but correlates to a worse OS, both in univariate and multivariate analysis. This is an intriguing observation for which we could formulate two non-mutually exclusive hypotheses: (i) presentation to a NETSARC MDTB is correlated to additional negative prognostic parameters not yet characterized and then not integrated in the multivariate model; (ii) this patient population has complex clinical characteristics requiring experienced surgical teams. Supplementary Figure S1 (available at *Annals of Oncology* online) shows that patient population presented to a NETSARC MDTB but not operated in a NETSARC center is at higher risk of relapse, but represents also the population at highest risk of death, even higher than the patient population which was not presented to an MDTB and not operated in NETSARC.

Thirty-six percent of patients operated in NETSARC centers had not been presented before surgery in the MDTB. While this was observed more often in small < 3 cm tumors and visceral sites (not shown), these figures must be improved. A research program is ongoing to understand these situations.

These observations indicate that presentation to a specialized MDTB cannot be the single recommended measure, and does not constitute a sufficient organizational process for sarcoma patients, if the subsequent surgery was not carried out in a NETSARC reference center. Overall, this analysis shows that two core components, presentation to a specialized sarcoma MDTB and surgical management, must be conducted in a NETSARC center to achieve optimal tumor control and survival in sarcoma patients in this country. Presentation to a specialized MDTB, while surgery is not carried out in a reference center is actually associated with the worst survival in this series. Guidance for the treatment from reference centers to non-expert centers is not sufficient and execution of the treatment by reference centers is needed to improve patient survival. Importantly, consistent results were recently reported in other countries with different health care systems [14, 29]: management in reference centers in The Netherlands and in Spain is associated with an improved outcome. This shows that the organized management in reference center for sarcoma may be able to improve survival of sarcoma patients regardless of the health care system.

Several preexisting conditions strongly influenced the risk of relapse and survival in this nationwide study. Previous cancer, previous RT, and most importantly a history of NF1 are correlated with an increased risk of local relapse, progression, and worse survival in univariate analysis. Importantly, the two latter parameters were retained in multivariate analysis, as independent prognostic factors for local relapse (for previous RT) and for all three parameters (NF1). Actually NF1 was identified as one of the strongest adverse parameter for LRFS, EFS, and OS. This observation had not been previously reported in such a large national series and point out to explore innovative strategies, possibly specifically targeting the activated biological pathway in addition to classical treatments.

This series has several limitations: the limited follow-up, a lack of exhaustivity in the first years of network operations, and the proportion of patients with unspecified information. It is planned to expand progressively the numbers of mandatory field, which must be completed to upload the clinical case to improve the latter issue. The description of pre- and postoperative treatment is also very limited. It is important to mention that this study is not a clinical trial. A regular and systematic update of the follow-up of these patients will be important to explore patient outcome for the longer term. Nevertheless, this series is to our knowledge among the largest prospective series of sarcoma patients collected at a national level. Importantly, it is close to exhaustivity since 2013, based on the expected incidences of these tumors. These results provide a tangible confirmation of the statements proposed in clinical practice guidelines for sarcomas: treatment carried out from the initial surgical steps in reference centers offers a greater chance of disease free and OS in sarcoma. These results show that early referral, management, and treatment in reference center improve the quality of initial surgery, reduce the risk of reoperation, and improve survival to a magnitude never achieved with any new therapeutic intervention. This management may also occur at a lower overall treatment cost [23, 24]. These observations are likely to be relevant to other rare cancers, which altogether represent 20% of all cancers and often share the same management issues [30, 31]. The worse survival reported in many series is better understood based on the present results.

In conclusion, these results show that the management of patients with sarcomas must be carried out by a multidisciplinary team with experience in the management of sarcoma, from the diagnostic phase, before any treatment initiation, and for at least

the first surgical treatment. When the management is not done in reference centers, clinical practice guidelines, are less frequently applied, with an increased risk of relapse, reoperation, and death. This study also identifies NF1 as a major adverse prognostic factor increasing the risk of relapse and death to a larger magnitude than any other parameter in non-metastatic patients.

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