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ORIGINAL ARTICLE

## Improved nationwide survival of sarcoma patients with a network of reference centers

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**Background:** We investigated the impact of the implementation of a network of reference centers for sarcomas (NETSARC) on the care and survival of sarcoma patients in France since 2010.

**Patients and methods:** NETSARC ([netsarc.org](http://netsarc.org)) is a network of 26 reference sarcoma centers with specialized multidisciplinary tumor boards (MDTBs), funded by the French National Cancer Institute (INCa) since 2010. Its aims are to improve the quality of diagnosis and care of sarcoma patients. Patients' characteristics, treatments, and outcomes are collected in a nationwide database. The objective of this analysis was to compare the survival of patients in three periods: 2010-2012 (non-exhaustive), 2013-2015, and 2016-2020.

**Results:** A total of 43 975 patients with sarcomas, gastrointestinal stromal tumors (GISTs), or connective tissue tumors of intermediate malignancy were included in the NETSARC+ database since 2010 (n = 9266 before 2013, n = 12 274 between 2013 and 2015, n = 22 435 in 2016-2020). Median age was 56 years, 50.5% were women, and 13.2% had metastasis at diagnosis. Overall survival was significantly superior in the period 2016-2020 versus 2013-2015 versus 2010-2012 for the entire population, for patients >18 years of age, and for both metastatic and non-metastatic patients in univariate and multivariate analyses ( $P < 0.0001$ ). Over the three periods, we observed a significantly improved compliance to clinical practice guidelines (CPGs) nationwide: the proportion of patients biopsied before surgery increased from 62.9% to 72.6%; the percentage of patients presented to NETSARC MDTBs before first surgery increased from 31.7% to 44.4% ( $P < 0.0001$ ). The proportion of patients with R0 resection on first surgery

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increased (from 36.1% to 46.6%), while R2 resection rate decreased (from 10.9% to 7.9%), with a better compliance and improvement in NETSARC centers.

**Conclusions:** The implementation of the national reference network for sarcoma was associated with an improvement of overall survival and compliance to guidelines nationwide in sarcoma patients. Referral to expert networks for sarcoma patients should be encouraged, though a better compliance to CPGs can still be achieved.

**Key words:** sarcoma, network, reference centers, multidisciplinary tumor board, clinical practice guidelines, survival

## INTRODUCTION

Clinical practice guidelines (CPGs) for sarcomas almost universally recommend that diagnostic and therapeutic procedures should be conducted in reference centers with multidisciplinary expertise and that patients with a suspected diagnosis should be referred to a sarcoma center before any treatment.<sup>1-8</sup>

The rationale for such a systematic referral is based on several considerations. At the diagnostic stage, because of the histological and molecular diversity, as well as rarity of sarcomas,<sup>9-11</sup> these tumors are often misdiagnosed when not reviewed by a pathology expert center,<sup>12-17</sup> resulting in potential inadequate treatments and poor outcome. Central pathology review has been reported to be cost-effective in sarcomas.<sup>15-17</sup>

Optimal surgical removal of sarcomas, with *en bloc* R0 resection, is the mainstay of the curative treatment of localized disease.<sup>1-8</sup> The quality of initial surgery is a major prognostic factor for recurrence-free survival and overall survival in all series. For sarcomas, inadequate diagnostic procedures and treatment, e.g. unscheduled surgery and incomplete resection of the localized primary tumor without initial biopsy, are observed in a higher proportion of patients treated in non-specialized primary care centers.<sup>18-23</sup> Often qualified as ‘whoops’ procedures,<sup>18</sup> inadequate initial diagnosis and management often results in an increased risk of relapse and death, a need for re-excision, additional therapeutic procedures, and increased costs.<sup>24-45</sup>

Since 2010, the French National Cancer Institute (INCa) supported the creation and implementation of the NETSARC network of reference sarcoma centers.<sup>10,37-42</sup> NETSARC records all incident sarcomas and connective tissue tumor cases in the common database [netsarc.org](https://www.netsarc.org) or [bcbsarcoma.org](https://www.bcbsarcoma.org), after confirmation of diagnosis by central pathology review. Patient management procedures and outcomes are collected. With an overall stable incidence per year since 2013, often superior to previous publications, this database is considered close to exhaustive.<sup>10,13-17,46,47</sup> This offers the opportunity to evaluate the real-life impact of the organization of reference centers on patient survival at a nationwide level.

In the present article, we report on the survival of the population of patients with sarcoma diagnosed in France since 2010, comparing three periods, 2010-2012, 2013-2015, and 2016-2020, the last two being considered as close to exhaustive.

## PATIENTS AND METHODS

### The network

The INCa supported the implementation of a clinical network for sarcomas (NETSARC) in 2009, which was launched in January 2010 ([Appendix 1](#)). This network is missioned to improve the management and outcome of sarcoma patients. Twenty-six reference centers were designated in this clinical network. NETSARC was linked to a sarcoma pathological reference network RRePS (‘Network for expert pathology diagnosis in sarcomas of 23 reference centers for sarcomas pathology in charge of the centralized histological review of each suspected case of sarcoma’) and to the RESOS network (reference center for the diagnosis and treatment of bone sarcomas). All three were merged in 2018 within the NETSARC+ network which now conducts all these activities, in particular the management of the common database ([sarcomabcb.org](https://www.sarcomabcb.org)). This database gathers all cases of sarcomas with confirmed pathological diagnosis after central expert review, all cases presented in multidisciplinary tumor boards (MDTBs) within the network, and describes their diagnosis, patient and tumor characteristics, therapeutic management, and outcome.

### Centers

Reference centers designated in this network must have a dedicated multidisciplinary team, with expert pathologists, radiologists, surgeons, radiation oncologists, medical oncologists, nuclear medicine specialists, molecular biologists, and pediatricians. Participation to the educational and research activities of the French Sarcoma Group is requested, as well as weekly MDTBs dedicated to sarcomas. A threshold level of activity (e.g. number of incident patients) is not requested in NETSARC+, in contrast to multinational networks, e.g. European Reference Network EURACAN, in which a threshold of 100 new patients managed per year is recommended.<sup>48</sup> All sarcoma patient cases discussed in MDTBs within NETSARC centers are recorded in the database, by a dedicated team of clinical research assistants, supervised by three coordinating centers (Centre Leon Berard, Gustave Roussy, Institut Bergonié). Patient files may be presented by the primary care physician at any time of patient journey, e.g. 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. Patient and treatment data are prospectively included and regularly updated by the study coordinators.

Monitoring of the centers is carried out by the three coordinating centers on a regular basis.

### The NETSARC database

The NETSARC+ database ([sarcomabcb.org](http://sarcomabcb.org)) provides a close to exhaustive description of the incident and prevalent population of sarcoma patients in France, with the pathological review activity and the clinical activity. It provides a description of the diagnostic and patient characteristics, of initial treatment procedures, and of patients' outcomes, in particular survival and relapse. The database includes a limited set of data, on purpose, to enable the exhaustive collection of new patients and update of previous patients with limited means. The center which carried out the first resection is documented, as well as the quality of surgery (R0, R1, R2, unknown), re-excision, and the center where re-excision was carried out. All data presented here were extracted from the [sarcomabcb.org](http://sarcomabcb.org) database accessible online.

### Statistical analysis

The categorical data were summarized by the frequencies and percentages, and the continuous covariates were summarized with median, range, and number of observations. The statistical test used for comparison was chi-square (or a Fisher's) test for categorical covariates. A Kruskal–Wallis test was used for covariates with more than two ordered categories or for continuous variables. The diagnostic date is the date of histological diagnosis (after biopsy or first surgery). Overall survival is calculated from the date of diagnosis to the date of last follow-up or death. Survival curves were plotted using a Kaplan–Meier method and compared using the log-rank test. Univariate and multivariate analyses for survival included (i) classical prognostic factors for sarcoma (sex, age, grade, tumor size, site, depth, presence of metastasis, etc.), and (ii) management characteristics with a prognostic impact on survival (biopsy before surgery, adequate imaging, MDTB before treatment, etc.). Cox proportional hazards model was used for the multivariate analysis, introducing parameters significant 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  $>0.05$  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 1 error ( $P \geq 0.05$ ). All statistical tests were two-sided. All statistical analyses were carried out using SPSS (version 23.0; IBM France; Bois-Colombes, France).

## RESULTS

### Patient population

Among the 55 526 patients with sarcomas present in the database at the time of the analysis, 43 975 patients with sarcomas, GISTs, or connective tissue tumors of intermediate malignancy included in the NETSARC+ database were

diagnosed between 2010 and 2020 (Table 1). There were 9266 patients included before 2013, 12 274 between 2013 and 2015, and 22 435 in 2016–2020. Median age of the series was 56 years (range), 50.5% were women, and 13.2% were metastatic at diagnosis (Table 1). The three most frequent histotypes were liposarcomas, leiomyosarcomas, and undifferentiated pleomorphic sarcomas. The proportion of metastatic patients as well as the size of the primary tumor were significantly larger in the first period (2010–2012), but not significantly different between periods 2013–2015 and 2016–2020. The other clinical characteristics of the patients were overall similar between the three periods (Table 1).

### Survival

The primary objective of this study was to describe and compare the survival of patients in the different time periods since the creation of the network: (i) 2010–2012, where exhaustivity was not reached ( $\sim 4.7/10^5/\text{year}$ ); (ii) 2013–2015 from where yearly pathology review has provided stable incidence figures ( $\sim 6.2/10^5/\text{year}$ ); and (iii) the more recent 2016–2020 period ( $\sim 6.6/10^5/\text{year}$ ). With a median follow-up of 14 months in the whole series, the overall survival was found significantly superior in the population of patients diagnosed in the period 2016–2020 versus 2013–2015 versus 2010–2012 in the whole population of 43 975 patients (Figure 1,  $P < 0.0001$ ).

Comparison of survival in the two most recent periods where exhaustivity was reached also showed a superior survival for all patients in the 2016–2020 versus 2013–2015 period {hazard ratio (HR) = 0.82 [95% confidence interval (CI) 0.77–0.87]}, for patients aged  $\geq 18$  years [HR = 0.81 (95% CI 0.76–0.86)], and for both metastatic [HR = 0.68 (95% CI 0.61–0.77)] and non-metastatic patients [HR = 0.81 (95% CI 0.75–0.88)] (Figure 1,  $P < 0.0001$  for all). At 12 months from diagnosis, survival rates were 92.7% in the 2016–2020 period versus 90.4% in the 2013–2015 period, i.e. a 24% reduction of the relative risk of death for 2016–2020. In univariate analysis, survival was found superior in the most recent period for all most common histotypes but GIST (Supplementary Figure S1, available at <https://doi.org/10.1016/j.annonc.2024.01.001>).

In multivariate analysis, female gender, younger age, lower grade, absence of metastasis at diagnosis, and the most recent period (2016–2020) were found to be independent favorable prognostic factors, while size reported  $>10$  cm, specific histotypes, and visceral sites were associated with a worse survival (Table 2).

### Management of the patients in the three periods

In order to explain this survival improvement, we measured the compliance to international CPGs over time in this nationwide population. Over the three periods (2010–2012, 2013–2015, 2016–2020), the percentage of patients with a documented diagnostic biopsy before treatment increased from 62.9% (5832/9266) to 65.3% (8012/12 274) to 72.6% (16 571/22 435) nationwide ( $P < 0.001$ ) (Table 1). This

Table 1. Description of patients and sarcomas in the three periods				
	Period			Total <i>n</i> = 43 975
	2010-2012 <i>n</i> = 9266	2013-2015 <i>n</i> = 12 274	2016-2020 <i>n</i> = 22 435	
Age at diagnosis (years)				
Mean (SD)	55.48 (19.42)	55.71 (20.24)	56.50 (20.59)	56.07 (20.26)
Q1-Q3	42.00-70.00	42.00-71.00	43.00-72.00	42.00-72.00
Age at diagnosis (years), <i>n</i> (%)				
0-29	1148 (12.4)	1588 (12.9)	2861 (12.8)	5597 (12.7)
30-59	3653 (39.4)	4709 (38.4)	8106 (36.1)	16 468 (37.4)
60-79	3692 (39.8)	4760 (38.8)	9061 (40.4)	17 513 (39.8)
≥80	773 (8.3)	1217 (9.9)	2407 (10.7)	4397 (10.0)
Sex, <i>n</i> (%)				
Female	4726 (51.0)	6183 (50.4)	11 291 (50.3)	22 200 (50.5)
Male	4540 (49.0)	6091 (49.6)	11 144 (49.7)	21 775 (49.5)
Tumor size (mm)				
Mean (SD)	94.36 (75.1)	92.77 (81.4)	91.62 (73.6)	92.52 (76.22)
Q1-Q3	42.00-125.00	40.00-120.00	40.00-120.00	40.00-120.00
>100 mm, <i>n</i> (%)	2588 (32.3)	3395 (31.8)	6014 (31.3)	11 997 (31.7)
Grade, <i>n</i> (%)				
1	660 (7.1)	786 (6.4)	1243 (5.5)	2689 (6.1)
2	1403 (15.1)	1724 (14.1)	3441 (15.3)	6568 (14.9)
3	3089 (33.3)	4012 (32.7)	6643 (29.6)	13 744 (31.3)
Missing data	696 (7.5)	1025 (8.4)	2205 (9.8)	3926 (8.9)
Non-gradable	3418 (36.9)	4727 (38.5)	8903 (39.7)	17 048 (38.8)
Histotype, <i>n</i> (%)				
GIST	700 (7.6)	931 (7.6)	1731 (7.7)	3362 (7.6)
Leiomyosarcoma	1137 (12.3)	1431 (11.7)	2345 (10.5)	4913 (11.2)
Liposarcoma	1161 (12.5)	1507 (12.3)	2768 (12.3)	5436 (12.4)
Undifferentiated sarcoma	1013 (10.9)	1348 (11.0)	2970 (13.2)	5331 (12.1)
Other	5255 (56.7)	7057 (57.5)	12 621 (56.3)	24 933 (56.7)
Site of tumor, <i>n</i> (%)				
Bone	1346 (14.5)	1852 (15.1)	3184 (14.2)	6382 (14.5)
Soft tissue	6010 (64.9)	7799 (63.5)	14 158 (63.1)	27 967 (63.6)
Viscera	1906 (20.6)	2623 (21.4)	5085 (22.7)	9614 (21.9)
Metastatic at diagnosis, <i>n</i> (%)				
Yes	1220 (14.2)	1460 (13.0)	2634 (12.8)	5314 (13.2)
Biopsy first, <i>n</i> (%)				
No	3434 (37.1)	4262 (34.7)	6264 (27.4)	13 950 (31.0)
Yes	5832 (62.9)	8012 (65.3)	16 171 (72.6)	30 015 (69.0)

GIST, gastrointestinal stromal tumor; SD, standard deviation.

proportion was higher in patients operated in the NETSARC network, from 80.2% (2487/3103) to 82.7% (3578/4328) to 87.3% (6349/7068) in the three periods within NETSARC centers, versus from 40.6% (1722/4246) to 36.3% (3678/4342) to 52.80% (4382/8299), respectively, outside NETSARC centers ( $P < 0.0001$  for intra- and intergroup comparisons). The proportion of patients with unscheduled surgery without prior biopsy thus decreased nationwide in the last 10 years. The proportion of patients with preoperative imaging according to guidelines increased both numerically and in proportion over the periods [5191/7380 (70.3%) versus 7025/9504 (73.9%) versus 12 371/15 807 (78.3%),  $P < 0.0001$ ].

We then analyzed the quality of treatment decision process for these patients in the three periods focusing on the population of patients with documented surgery, i.e. 7380/9266 (79.6%) patients included before 2013, 9504/12 274 (77.4%) between 2013 and 2015, 15 807/22 435 (70.4%) in 2016-2020. Of note, a superior survival is also observed in patients without documented surgery

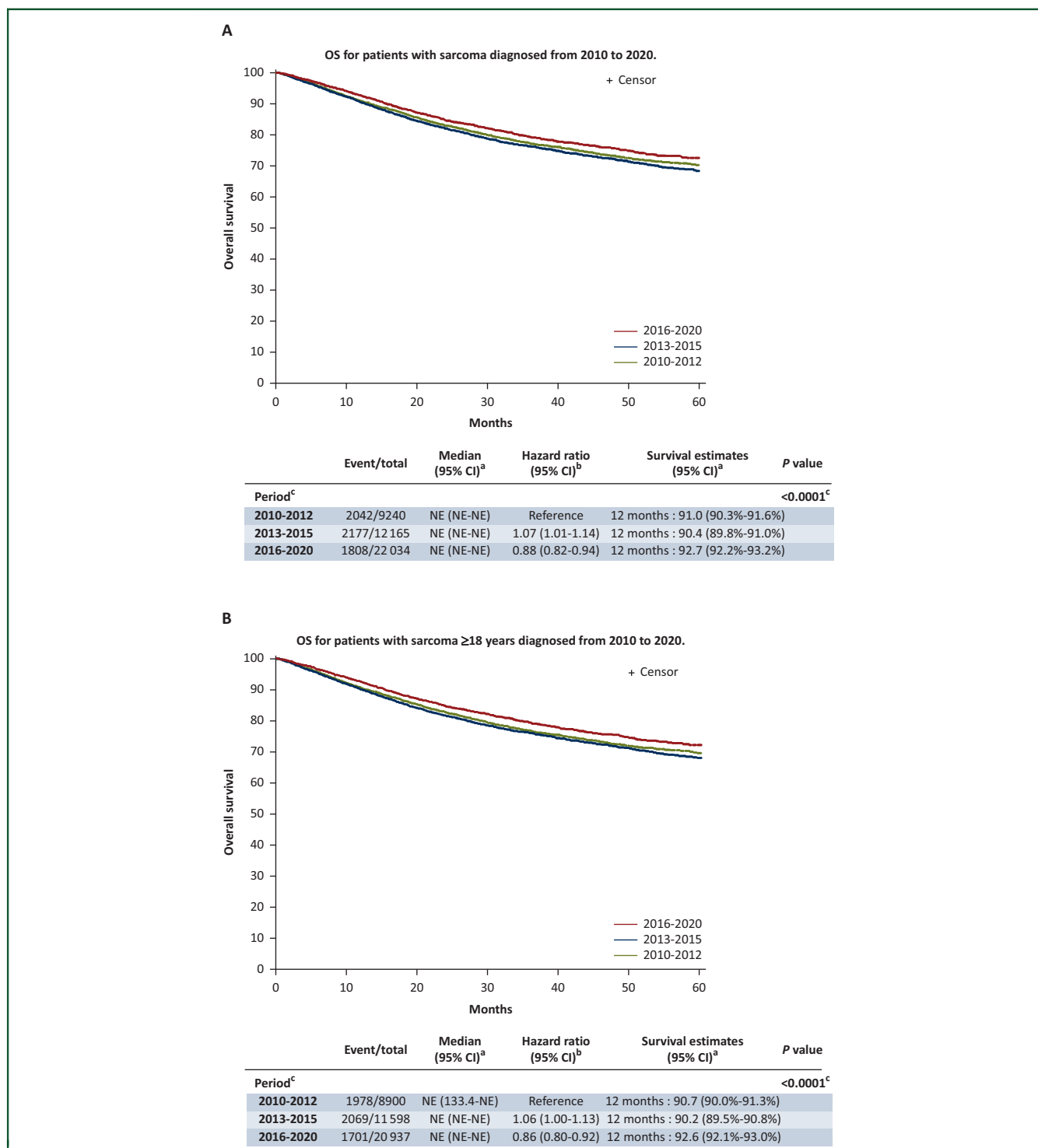
(Supplementary Figure S2, available at <https://doi.org/10.1016/j.annonc.2024.01.001>). In the group of patients with documented surgery, the nationwide proportion of patients presented to a NETSARC MDTB before surgery increased from 31.7% (2346/7380) to 39.1% (3714/9504) to 44.4% (7012/15 807) over the three periods ( $P < 0.001$ ). This proportion increased significantly (57.3% versus 70.3% versus 81.8%,  $P < 0.001$ ) within NETSARC centers in the three periods, but remained stable and low in patients operated outside NETSARC centers (13.3% versus 12.9% versus 13.5%,  $P = 0.63$ ).

The quality of surgery as evaluated by the proportion of R0, R1, R2, and R status unknown (R unk) increased significantly over the three periods, in the entire series, in the group of patients treated in NETSARC centers, and in the group of patients treated outside NETSARC centers (Table 3, chi-square  $P < 0.0001$ ). However, for the latter, the proportion of patients in whom R0 resections were achieved was 34.6% only in the latest period versus 60.2% for the group of patients operated in



NETSARC centers. The proportion of patients with R2 resection was 12.9% outside NETSARC versus 1.9% inside NETSARC in the latest period ( $P < 0.0001$  for both). The proportion of patients with R unk resection was 29.3% outside versus 14.8% inside NETSARC in the latest period ( $P < 0.0001$ ) (Table 3).

Finally, we analyzed the proportion of patients re-operated after a first surgery. Re-operation is generally proposed to patients with R2 resection and fragmented resection, and for some centers after R1 or even R0 resection carried out outside reference centers.<sup>35,36</sup> Overall, 44.4% (1301/2931) of patients with first R2 surgery, 26.9%



**Figure 1. Overall survival of sarcoma patients in the three different periods.** (A) All patients, (B) patients aged ≥18 years, (C) patients aged ≥18 years without metastasis at diagnosis, (D) patients aged ≥18 years with metastasis at diagnosis. The median follow-up for the three periods are 40, 27, and 10 months for 2010-2012, 2013-2015, and 2016-2020, respectively. CI, confidence interval; NE, not estimable. <sup>a</sup>Kaplan–Meier method. <sup>b</sup>Cox model. <sup>c</sup>Log-rank test.

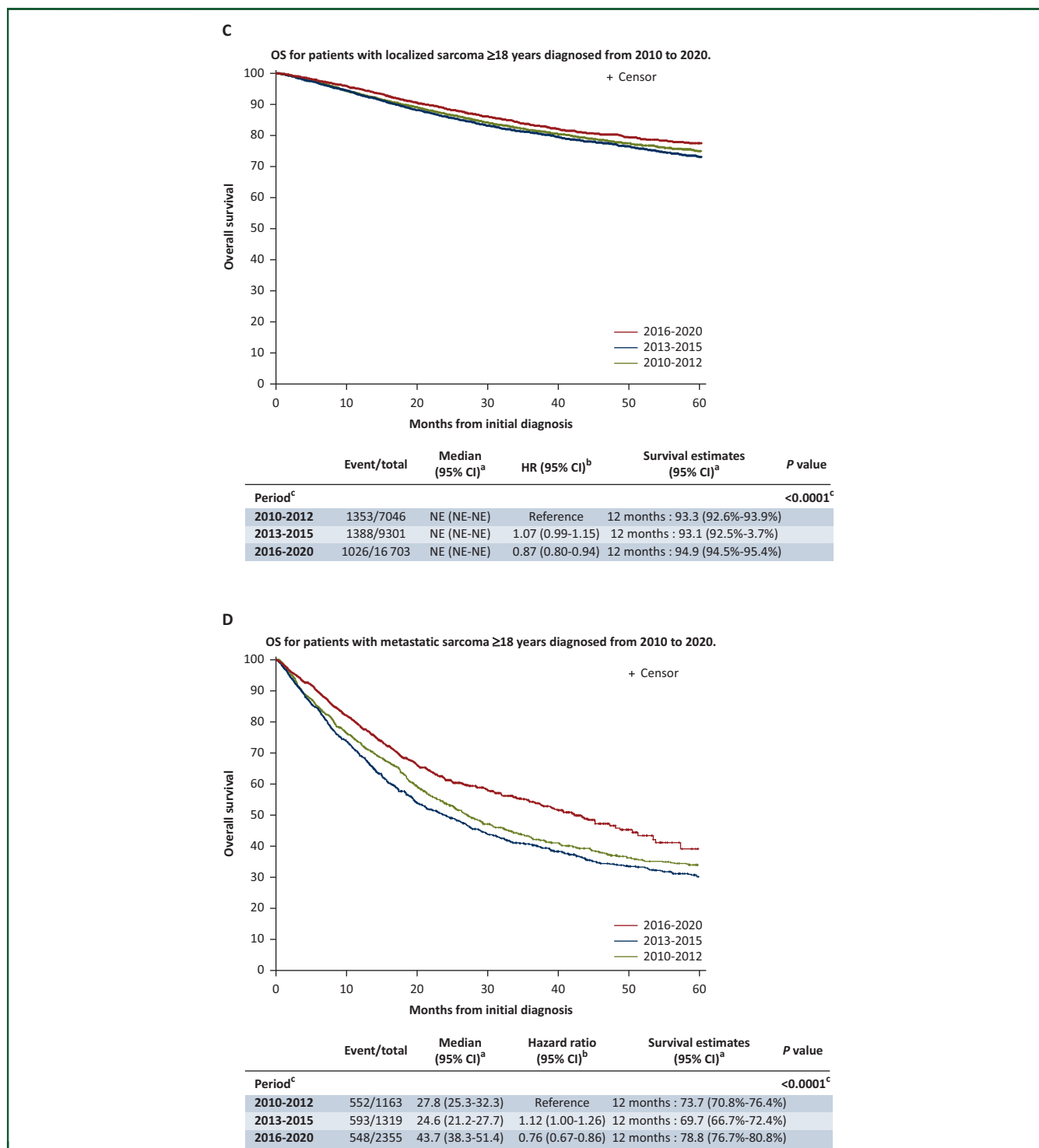


Figure 1. Continued.

(2163/8016) of patients with a first R1 surgery, 3.8% (528/13 275) of patients with first R0 surgery, and 11.6% (925/7942) of R unk were re-excised. The proportion of patients re-operated after first surgery decreased nationwide from 16.6% to 13.7% in the three periods ( $P < 0.0001$ ). This reduction was also significant in NETSARC centers (from 9.0% to 5.4%,  $P < 0.0001$ ) but marginally significant outside NETSARC centers (from 22.3% to 21.6%,  $P = 0.012$ ) (Table 4).

## DISCUSSION

Sarcomas are a group of rare to ultrarare cancers for which multidisciplinary management in a reference center is recommended in all CPGs.<sup>1-8</sup> However, most sarcoma patients are not managed in reference centers worldwide. The organization of sarcoma treatment in networks of reference centers was proposed first by the Scandinavian sarcoma group in Scandinavian countries.<sup>24-26,28-31</sup> Since then, several countries have organized national sarcoma groups

**Table 2. Multivariate analysis of prognostic factors for survival (n = 43 975 patients)**

Parameters	Hazard ratio	95% Hazard ratio confidence limits	P value
Age at diagnosis	1.02	1.02-1.03	<0.0001
Male sex	1.23	1.16-1.30	<0.0001
Grade			
Grade III	1.95	1.81-2.10	<0.0001
NA	0.67	0.60-0.73	<0.0001
Histotype (ref = other)			
GIST	0.38	0.32-0.45	<0.0001
Liposarcoma	0.81	0.73-0.90	<0.0001
Malignant peripheral nerve sheath tumor	3.63	3.04-4.33	<0.0001
Myxofibrosarcoma	0.66	0.55-0.78	<0.0001
Rhabdomyosarcoma	1.95	1.71-2.21	<0.0001
Synovial sarcoma	1.65	1.42-1.91	<0.0001
Tumor size >10 cm	1.47	1.38-1.56	<0.0001
Site of tumor			
Bone (ref = viscera)	0.92	0.84-1.01	0.0945
Soft tissue (ref = viscera)	0.71	0.66-0.77	<0.0001
Metastatic at diagnosis (ref = no)	3.72	3.49-3.96	<0.0001
Time period 2016-2020 (ref = 2010-2015)	0.78	0.73-0.83	<0.0001

Cox model was carried out including all significant variables in univariate analysis and using a backward selection procedure which entails including all the covariates in the model and removing those whose P value is >0.05 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 1 error (P ≥ 0.05). GIST, gastrointestinal stromal tumor; NA, not applicable.

and/or reference centers and networks.<sup>27-45</sup> In most countries, such as France, the diagnosis and treatment of patients with sarcoma can be carried out in any oncology facility. In others, such as Scandinavian countries or the UK,<sup>24-26</sup> the management of sarcoma patients must be carried out in dedicated reference centers.

We report here on the impact of implementing a network of reference centers for sarcoma treatment at a global level on patient survival in a nation of ~66 million inhabitants.

The question addressed in this research was whether the implementation of a network of reference centers for

sarcomas in a country where the diagnosis and care of sarcoma patients is not centralized had a measurable impact on patient survival. The central pathology review implemented by the INCa is mandatory in order to obtain full financial coverage for the costs of treatment care. This enabled to identify all cases of sarcomas nationwide since 2010, with a ramp-up period of 3 years. All patients were included in the national database of NETSARC.<sup>10</sup> Sarcoma patients and their characteristics were identified. Their treatment and follow-up are documented for the majority of cases.

**Table 3. Quality of surgery nationwide in the three periods within and outside reference centers**

Quality of first surgery	Patients, n (%)				Chi-square P value
	2010-2012	2013-2015	2016-2020	Total	
<b>NETSARC</b>					
R0 margin	1593 (51.3)	2377 (54.7)	4388 (61.1)	8358 (57.1)	
R1 margin	757 (24.4)	1049 (24.2)	1596 (22.2)	3402 (23.3)	
R2 margin	158 (5.1)	177 (4.1)	135 (1.9)	470 (3.2)	
Unknown	600 (19.3)	739 (17.0)	1061 (14.8)	2400 (16.4)	
Total	3108	4342	7180	14 630	<0.0001
<b>Outside NETSARC</b>					
R0 margin	1073 (25.1)	1387 (26.9)	2985 (34.6)	5445 (30.1)	
R1 margin	1200 (28.1)	1415 (27.4)	1999 (23.2)	4614 (25.5)	
R2 margin	643 (15.1)	701 (13.6)	1117 (12.9)	2461 (13.6)	
Unknown	1356 (31.7)	1659 (32.1)	2526 (29.3)	5541 (30.7)	
Total	4272	5162	8627	18 061	<0.0001
<b>All patients</b>					
R0 margin	2666 (36.1)	3764 (39.6)	7373 (46.6)	13 803 (42.2)	
R1 margin	1957 (26.5)	2464 (25.9)	3595 (22.7)	8016 (24.5)	
R2 margin	801 (10.9)	878 (9.2)	1252 (7.9)	2931 (9.0)	
Unknown	1956 (26.5)	2398 (25.2)	3587 (22.7)	7941 (24.3)	
Total	7380	9504	15 807	32 691	<0.0001

This table describes the number and proportion of patients operated who benefited from a first R0, R1, R2, or R unk resection overall nationwide, within the reference centers, and outside reference centers.



Table 4. Re-excision rates nationwide in the three periods within and outside reference centers			
	Patients, n (%)		Chi-square P value
	Re-excision	No re-excision	
<b>All patients</b>			
Period			
2010-2012	1224 (16.6)	6156 (83.4)	
2013-2015	1510 (15.9)	7994 (84.1)	
2016-2020	2170 (13.7)	13 637 (86.3)	
Total	4904	27 787	<0.0001
<b>In NETSARC</b>			
Period			
2010-2012	288 (9.0)	2893 (90.9)	
2013-2015	314 (7.0)	4116 (93.0)	
2016-2020	429 (5.4)	7276 (94.6)	
Total	1021	14 335	<0.0001
<b>Outside NETSARC</b>			
Period			
2010-2012	936 (22.3)	6156 (77.7)	
2013-2015	1196 (23.8)	7994 (76.2)	
2016-2020	1751 (21.6)	6361 (78.4)	
Total	3883	13 452	0.012

This table describes the number and proportion of patients re-operated after a first surgery nationwide, within the reference centers, and outside reference centers.

The three periods were selected with the following rationale: (i) the first 5 years (2010-2015) and (ii) the last 5 years (2016-2020). The first 5-year period was split into two subperiods: (i) 2010-2012, where patient identification and inscription in the NETSARC database was not exhaustive and (ii) a second subperiod 2013-2015, where the incidence was similar to the second period of 5 years.

The population analyzed here is therefore a nationwide, representative population of patients with 13.2% of patients with metastasis at diagnosis and 10% of patients above 80 years. Such an inclusive population is usually not captured in clinical trials.

The series of this dataset is considered to be 'close to exhaustive' for the following reasons. With the current organization, central pathology review is mandatory nationwide. This ensures that the diagnosis is reviewed by expert pathologists and is therefore accurate. A diagnosis of sarcoma leads to a mandatory declaration to the National Social Security. A second layer of security for exhaustiveness is obtained at the time of the presentation to the MDTB for therapeutic decision. When the tumor sample of a patient was not previously centrally reviewed, this is organized later on, after the MDTB. There are therefore theoretically two possible situations which could preclude the patient to be identified in the network: (i) when the initial pathology diagnosis is not even suspected and (ii) if the diagnosis is suspected but the patient does not enter the health care system, because of clinical status or, e.g. the recent pandemic circumstances. For these reasons, we chose to mention close to exhaustive. Of note, because (i) the incidence of sarcomas within NETSARC was superior to that previously reported, and (ii) the incidence of sarcomas is stable over time in the last 10 years, the proportion of missed patients with sarcomas missed in the network is probably limited.

The results presented show that the survival of this nationwide series of sarcoma patients improved in the recent years. The improvement of survival was detected in univariate analysis for the 2016-2020 period, compared to the previous period (2013-2015) where the incidence was already at a plateau, as compared to the first period of NETSARC (2010-2012) where not all patient cases were collected. Diagnosis during the latest period was also an independent favorable prognostic factor along with classical prognostic factors of survival in sarcoma in the present study. Along with the improvement in the quality of care, the magnitude of reduction of the risk of death in the most recent period in multivariate analysis is HR 0.78. This is likely to result from a general improvement in standard therapeutic practices as recommended by CPGs, but the individual contribution of each steps of management is unclear. One can speculate that the improvement in the quality of resection is probably a major contributor to this observation. Superior survival in the most recent period was observed for the most common histotypes of sarcomas in subgroup analysis (Supplementary Figure S1, available at <https://doi.org/10.1016/j.annonc.2024.01.001>). Survival was similar in the three periods for the GIST subgroup, but was very high already in the first period. Adjuvant imatinib for high-risk GIST was available at the beginning of NETSARC in 2010. It is important to mention here that the breadth of the dataset, and the limitation of size of the present article, does not allow to fully capture the potential heterogeneity of outcome for some histological subtypes, such as rhabdomyosarcomas; this will be the topic of future investigations.

Of note, the magnitude of improvement was larger in the metastatic patient population, as well as in the population of patients without documented surgery (Supplementary Figure S2, available at <https://doi.org/10.1016/j.annonc.2024.01.001>), possibly because of the increase in the number of therapeutic options for advanced patients in the last 13 years, with new cytotoxics, targeted treatment, and local treatments [cryoablation, radiotherapy (RT), and high-intensity focused ultrasound for metastatic lesions].

The causality link between this temporal improvement in overall survival and the implementation of the NETSARC network of reference centers must of course be considered with prudence.

We analyzed during this period which were the major changes in patients' management, related to NETSARC implementation. During this time period, the proportion of patients presented to the NETSARC MDTB before any treatment decision improved regularly (not shown), a parameter previously found to be associated with a reduction in relapse.<sup>33,34</sup> Here, the compliance to CPGs for standard diagnostic procedures and for the first therapeutic phase improved significantly over time, nationwide. We observed a nationwide reduction of the proportion of patients operated without biopsy ('whoops operations'),<sup>43-48</sup> and a reduction of the proportion of patients without proper imaging. Importantly, these improvements were observed both in reference centers and outside reference

centers, although the proportion of non-CPG-compliant practices was significantly superior outside reference centers. NETSARC centers communicate widely with their regional networks and general practitioners for each individual patient and organize regular meetings regionally and nationally as part of continuous medical education activities. We interpret this global improvement as a consequence of the 10 years of regular training and communication to the primary care physicians, radiologists, and surgeons for each individual patient, along with university courses in medical schools. The improvement of the quality of care observed in reference centers also shows the need for continuous practice monitoring within expert reference centers.

The most significant improvement in practice is the quality of surgery nationwide, within NETSARC centers, but also, though to a lower extent, outside NETSARC centers. Again, the overall quality of surgery is significantly superior in the NETSARC centers versus non-reference centers, with two times more R0 resections and six times less R2 resections. This general improvement has probably a major role in the survival improvement observed in the recent years, as R0 resections are associated with the best survival, while R2 resections or R unk resections are associated with a high risk of relapse and death.<sup>1-8</sup> The improvement in the quality of first resection is likely to account for the reduction of the rate of re-resection in the database. The role and indications of re-excision after a first surgery are debated.<sup>1-8,35,36</sup> Indications considered for re-excisions are generally incomplete R2 surgery, and for some centers, a first R1 resection, or even a first unplanned but R0 resection outside a reference center. The overall rate of re-excision decreased significantly nationwide in the most recent period. This decrease was almost exclusively observed in NETSARC centers, consistently with the remaining high rate of R2 resections outside reference centers.

The improved quality of surgery is however unlikely to be the sole contributor to the observed superior survival. Of note, the precise details of adjuvant and neoadjuvant chemotherapy and RT are not consistently available in the NETSARC database, nor the participation to clinical trials.<sup>1-8</sup> While the details of adjuvant and neoadjuvant treatments are incomplete in the NETSARC dataset, the overall proportion of patients with documented neoadjuvant treatment decreased numerically from 19.2% to 20.0% to 17.5% in the most recent period. The use of neoadjuvant or adjuvant treatment is therefore unlikely to account for the superior survival observed in the most recent period. A better survival in the most recent period is observed in patients presenting with metastasis at diagnosis, with a larger magnitude, and also in patients who had no documented surgery. The increased proportion of patients treated in a multidisciplinary setting, with interventional radiology, stereotactic RT, novel cytotoxics, and targeted treatments adapted to the driver molecular alterations, may have contributed to this observation.<sup>1-8</sup>

Organization of patient management in reference centers in a country where this was not previously available was

associated with survival improvement of an important magnitude. The next step could be to organize a mandatory referral of all sarcoma patients to reference centers, as organized previously in Scandinavian countries and the UK. Such political decisions for the health care system would require an in-depth reinforcement of medical resources of these reference centers to be able to cope with the workload.

Our results should encourage this political decision, also supported by medico-economic studies reported before.<sup>15,16,34</sup> These decisions would likely be cost-effective, and should improve patients' survival to an unprecedented level. The medico-economic analysis of NETSARC which we previously reported indicated the cost-effectiveness of the central pathology review and the reduction of re-operations for patients operated in reference center.<sup>16,17,29</sup> An analysis of the cost-effectiveness of the entire organization of reference centers is ongoing. These results point to the importance of collecting exhaustive registries, carefully controlled and measured. These observations are also instructive for the European Reference Network actions for rare disease and rare cancers (EURACAN).<sup>48</sup>

This study has however important limitations. This is not a prospective clinical study. The control series is the nationwide population of sarcoma patients in the earlier period (2013-2015) when the database was considered as close to exhaustive. The database misses information on follow-up and clinical presentation for a fraction of patients: clinical and tumor parameters were not available for all patients, e.g. unknown grade in a fraction of patients. This is an obvious objective for the improvement for this network. Another limitation of the study is the limited follow-up of the three cohorts, and the intrinsic differences of follow-up in the three observation periods. We opted for this reason to comment conservatively on the survival at 1 year, at the time close to median follow-up. It is however noteworthy that beyond 1 year the survival of patients treated in the most recent period remained significantly above that of those of the previous cohort. Subsequent follow-up reports will be important to confirm this improvement in the years to come.

Nevertheless, this study provides a tangible confirmation in a nationwide population, most likely close to exhaustive, of the statements proposed in CPGs for sarcomas. As such, it has relevance to the management of most rare cancers, which altogether represent 20% of all cancers and often share the same management issues.<sup>43-45,48,49</sup> The mechanisms of their worse prognosis are well understood in view of the present results. Given the magnitude of improvement, these results indicate that organizing patients' management within reference centers is the best option to improve the individual and global survival of sarcoma patients, and shows the next steps to be accomplished to optimize patients' survival and reduce costs.

In conclusion, these results show that the survival of patients with sarcomas improved nationwide since the initiation of the NETSARC network, together with an improvement in both compliance to guidelines and quality

of surgery, inside and outside reference centers. Centralized management of rare cancer in reference centers is already in place in several countries. Central pathology review was found cost-effective and first surgery in reference centers reduces the need for secondary re-operation. Overall, management in reference centers is associated with improved patient survival. Such global regulation of care should be made mandatory in France to further improve patients' survival and reduce disease burden.

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### DISCLOSURE

The authors have declared no conflicts of interest.

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**APPENDIX 1****Acknowledgement**

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