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ORIGINAL ARTICLE – SARCOMA

Survival Benefit of the Surgical Management of Retroperitoneal Sarcoma in a Reference Center: A Nationwide Study of the French Sarcoma Group from the NetSarc Database

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ABSTRACT

Background. Guidelines recommend that retroperitoneal sarcoma (RPS) be managed in a reference sarcoma center (RSC), but the benefit remains to be demonstrated. This study investigated the impact of initial surgery performed within the NetSarc network on overall survival (OS).

Methods. NetSarc is a network of 26 RSCs with specialized multidisciplinary tumor boards (MDTs) that is funded by the French NCI. Since 2010, presentation to an MDT and second pathological review are mandatory for sarcoma patients, and data have been collected in a nationwide database. We extracted data for all patients who received surgery in or outside the network and who presented at a NetSarc center (NSC) for primary nonmetastatic RPS between 2010 and 2017.

Results. A total of 2945 patients were included: 1078 (36.6%) underwent the first surgery in an NSC, and 1867 (63.4%) in an out-of-network center. The median number of operations at an NSC during the study period was 23 (range: 3–209), and the corresponding median was 1 (range: 1–2) at out-of-network centers. The diagnostic procedures followed significantly more clinical practice guidelines within NetSarc, where there were significantly more first R0 resections [452 (41.9%) vs. 230 (12.3%)]. The OS was significantly superior for patients treated within NetSarc, with a 2-year OS of 87% vs. 70% ($p < 0.001$). In the multivariate analysis, surgery within an NSC was an independent predictor of OS, with a twofold lower odds ratio of death.

Conclusions. In this national study, surgery for primary RPS within an NSC was associated with a better OS.

Retroperitoneal sarcoma (RPS) is a rare malignancy, with an annual incidence of 0.76 new cases per 100,000 people.[1] Unlike extremity sarcoma, the mortality of RPS is mainly due to local recurrence, with up to 75% of deaths occurring in the absence of distant metastasis.[2] Efforts to standardize and improve the quality of surgery have been carried out over the past 10 years, with observations of

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better survival with more radical resection.[3–6] The standard of care is still surgery alone.[7,8] The results of the STRASS phase III, which randomized for preoperative radiotherapy or surgery alone, are awaited.[9] The results of retrospective studies are contradictory and possible biased.[10,11] Randomized studies of chemotherapy for RPS are lacking. However, resection is challenging given the usually large tumor size, the coexistence of well-differentiated and dedifferentiated areas that can incorrectly suggest a multifocal lesion and can lead to a piecemeal or incomplete surgery, the possible extension across anatomical borders, and the abutment or involvement of critical structures.[12] Referring patients for initial surgery is critical, because piecemeal resection and gross residual disease definitely jeopardize survival, and the results of surgery for recurrent RPS remain poor.[13–15] Furthermore, the benefit of reexcision after inadequate initial surgery is variable.[3,16] Consensus guidelines underline that RPS should be managed in a specialized reference center[17–19]; however, until now, studies have investigated the impact of hospital RPS case load on outcome, with the threshold being retrospectively defined.[17–19] The Gutierrez study mixed all sarcoma sites but highlighted that truncal sarcoma and RPS afforded a significantly better survival when treated at high-volume centers (HVCs), defined as having treated the upper third of the cases.[20] Three studies specifically analyzed the RPS site, although with a different definition of the threshold between low- and high-volume hospitals (LVHs and HVHs) or between academic and community centers.[21–23] In this study, we investigated the impact of the site of initial surgery in a reference sarcoma center as defined by the French National Cancer Institute.

PATIENTS AND METHODS

The Network

The French National Cancer Institute (INCa) promoted the creation of a clinical network for sarcoma (NetSarc) in 2010, with the mission to improve the management and outcome of sarcoma patients. Twenty-six reference centers in France were identified. Of them, 4 are University Hospitals, and 22 are cancer centers [all cancer centers in France are designated as NetSarc centers (NSCs)]. Identification was based on the presence of a multidisciplinary tumor board (MDT) consisting of sarcoma-specialized pathologist(s), radiologist(s), surgeon(s), radiation oncologist(s), medical oncologist(s), orthopedist(s), and pediatrician(s) whose predominant activity was sarcoma. In parallel, a French sarcoma pathological reference network (RRePS "Network for expert pathology diagnosis in sarcoma") was in charge of the second histological review of each suspected case in France. Presentation to an MDT and second pathological review are mandatory for sarcoma patients.

NetSarc Database

The NetSarc database lists all patients who have soft tissue sarcoma (STS) confirmed by a pathologist of the RRePS network and/or discussed by a NetSarc MDT. Sarcoma cases can be recorded in the NetSarc database at any stage of the disease. The main objectives of NetSarc are to obtain an exhaustive description of the cases and prevalence of sarcoma patients in France by cross-comparison of the pathological review database (rreps.org) and the clinical database (netsarc.org), as well as to monitor patient outcomes, particularly survival and relapse. The database purposely includes a limited set of data, registered by a dedicated team of clinical research assistants, that describes patient and tumor characteristics, the diagnostic pathway, the center that performed the first resection (an NSC or outside the network), the type of surgery (one bloc/nonevaluable or piecemeal resection), the surgical margins classified according to the UICC "R" classification, and any relapse and survival outcomes.[24] Details on adjuvant treatments were not registered. Recurrence in the primary field was tagged as "local recurrence," and extra-abdominal recurrence or sarcomatosis were tagged as "metastasis." We extracted data for all patients who underwent surgery for primary nonmetastatic RPS between January 1, 2010 and January 1, 2017. Patients younger than aged 15 years, patients with desmoid tumors, and patients with gastrointestinal stromal tumor (GIST) were excluded. Patients were classified as operated on outside of an NSC based on the initial surgery location being outside of NetSarc, even if adjuvant primary treatments or recurrence treatments were performed within an NSC. With respect to regulatory procedures, the NetSarc database received authorizations from the Advisory Committee on Information Processing in Material Research in the Field of Health (CCTIRS) and the French Data Protection Authority (CNIL) No. 910390.

Statistical Analyses

Categorical data are summarized by the frequencies and percentages, and continuous covariates are summarized as the median, range, and number of nonmissing observations. The statistical test used for comparisons was a Chi square test for categorical covariates. The diagnostic date is the date of histological diagnosis (biopsy or first surgery). Overall survival (OS) was calculated from the date of diagnosis to the date of last follow-up or death. Local progression-free survival (LPFS) and metastatic relapse-

free survival (MRFS) were computed from the diagnostic date to the date of the last follow-up or the first local progression/recurrence/metastasis, respectively. Progression-free survival (PFS) was computed from the date of diagnosis to the date of the last follow-up or the date of the first local relapse, metastatic progression, or death, whichever occurred first. Survival curves were plotted using the Kaplan–Meier method. Survival was compared using the log-rank test. The univariate and multivariate analyses included age, gender, grade, size, histological type, and preexisting conditions, which are collected routinely in the NetSarc database.[25] We also analyzed patients' presentation to a NetSarc MDT before versus after the first surgery and whether the primary surgery performed in an NSC affected patient outcomes. A Cox proportional hazard model was used for the multivariate analysis, introducing parameters that were significant in the univariate analyses. All statistical tests were two-sided. All statistical analyses were performed using SPSS (version 22.0).

RESULTS

Patient Characteristics

Between January 1, 2010 and January 1, 2017, a total of 2945 patients were operated on for primary RPS, and specimens were systematically reviewed in RRePS and/or registered in the NetSarc database. Among them, 1078 (36.6%) patients underwent the first surgery in a referral NSC, and 1867 (63.4%) in an out-of-network center. During the study period, the proportion of patients operated on at an NSC increased from 28% (2010) to 44% (2017). The median number of patients operated on within each NSC during the study period was 23 (range 3–209), whereas the median was 1 (range 1–2) at centers outside of NetSarc. Four cancer centers out of 26 NSCs in NetSarc accounted for the operations on 541 (50.2%) patients. These four centers were responsible for 18.3% of all RPS operations during the study period, with a median annual RPS volume of 17 patients. Patient demographics and clinical characteristics in and outside NetSarc are detailed in Table 1. Overall, RPS operations in an NSC often had less favorable features, with a higher proportion of grade 2 or 3 sarcoma ($p < 0.001$; Table 1). The characteristics of patients operated on in the 13 NSCs with the largest accruals versus the others were not significantly different; however, there was a trend for more grade 3 cases and larger tumors in the former group (data not shown).

Diagnostic Pathway

The diagnostic pathway was significantly more frequently in agreement with the clinical practice guidelines (CPGs) when the first surgery was performed within an NSC.[7] A higher number of patients who underwent surgery at an NSC had adequate tumor imaging before treatment ($p < 0.001$; Table 1). Percutaneous preoperative biopsy before surgery was performed more frequently for patients operated on at an NSC [852 (79%) patients vs. 1011 (54.2%) patients ($p < 0.001$)]. A greater proportion of patients who received surgery at an NSC were presented to a NetSarc MDT before surgery [552 (51.2%) patients vs. 557 (29.8%) patients ($p < 0.001$)].

Quality of Surgical Resection

The quality of the primary surgery performed in an NSC was significantly better, with more R0 resections [452 (41.9%) vs. 230 (12.3%)], fewer R2 resections [48 (4.5%) vs. 172 (9.2%)] and fewer piecemeal resections with nonevaluable or unknown margins [213 (19.7%) vs. 1132 (60.7%)] ($p < 0.001$; Table 1).

Survival

With a median follow-up of 22 months, the LPFS of patients treated at an NSC was significantly better than that of patients who received surgery outside the network, with a 2-year LPFS of 75% versus 55% (Fig. 1a; $p < 0.001$). Metastasis-free survival (MFS) and PFS also were significantly better when the first surgery was performed within an NSC (Fig. 1b; $p < 0.001$). OS was significantly improved when the first surgery was performed at an NSC, with a 2-year OS of 87% versus 70% (Fig. 1c; $p < 0.001$). Median OS, LPFS and PFS were not reached in the two groups. LPFS and OS were similar among the 13 NSCs with the largest accruals and among the 13 centers with lower accruals (Fig. 2a, b). In the multivariate analysis, surgery in an NSC was an independent predictor of OS, with a twofold lower odds ratio (OR) of death than that for surgery outside NetSarc (OR: 0.496, $p < 0.001$; Table 2). In the multivariate analysis, tumor size, grade, and histological subtype also impacted OS, LPFS, and PFS (Table 2), whereas adjuvant treatment did not.

DISCUSSION

In this nationwide series of patients from 2010 to 2017, we demonstrated that the risks of relapse and death of RPS were lower when the initial surgery was performed in an NSC, centrally defined by the French health authorities,

TABLE 1 Characteristics of patients, tumors, and treatments

Characteristics	All patients	First surgery performed in a NetSarc center		*p* value
	(*n* = 2945)	No (*n* = 1867)	Yes (*n* = 1078)	
Gender				0.169
Male	1489 (50.6)	962 (51.5)	527 (48.9)	
Female	1456 (49.4)	905 (48.5)	551 (51.1)	
Age at first diagnosis				
Median (range)	60.8 (15–94)			
Size of the tumor (cm)				0.087
< 10	2339 (79.4)	1468 (78.6)	871 (80.8)	
≥ 10	606 (20.6)	399 (21.4)	207 (19.2)	
Histology				
WD LPS	1292 (43.9)	787 (42.2)	505 (46.8)	0.014
DD LPS	544 (18.5)	294 (15.7)	250 (23.2)	< 0.001
LMS	468 (15.9)	319 (17.1)	149 (13.8)	0.021
Others	641 (21.8)	467 (25)	174 (16.2)	< 0.001
Grade				< 0.001
1	558 (19)	308 (16.5)	250 (23.2)	
2	937 (31.8)	548 (29.4)	389 (36.1)	
3	605 (20.5)	377 (20.2)	228 (21.2)	
NA	433 (14.7)	314 (16.8)	119 (11)	
Unknown	412 (14)	320 (17.1)	92 (8.5)	
Adequate imaging				< 0.001
Yes	2296 (78)	1340 (71.8)	956 (88.7)	
No	649 (22)	527 (28.2)	122 (11.3)	
Biopsy				< 0.001
Yes	1863 (63.3)	1011 (54.2)	852 (79)	
No	1082 (36.7)	856 (45.8)	226 (21)	
MDT consult before surgery				< 0.001
Yes	1109 (37.7)	557 (29.8)	552 (51.2)	
No	1836 (62.3)	1310 (70.2)	526 (48.8)	
Margins				< 0.001
R0	682 (23.1)	230 (12.3)	452 (41.9)	
R1	698 (23.7)	333 (17.8)	365 (33.9)	
R2	220 (7.5)	172 (9.2)	48 (4.5)	
Unknown or not evaluable	1345 (45.7)	1132 (60.7)	213 (19.7)	
Fragmented tumor				< 0.001
No	402 (13.6)	169 (9.1)	233 (21.6)	
Yes	88 (3)	67 (3.6)	21 (1.9)	
Unknown	2388 (81.1)	1591 (85.2)	797 (73.3)	
NA	67 (2.3)	40 (2.1)	27 (2.5)	
Median patients operated on/center		1 (1, 2)	23(3209)	< 0.001
Adjuvant treatment (RT or CT)				
Yes	208 (7%)	97 (5%)	11 (10.3%)	
No	888 (30%)	479 (26%)	409 (38%)	
Missing	1849 (63%)	1291 (69%)	558 (51.7%)	

DD LPS dedifferentiated liposarcoma, *LMS* leiomyosarcoma, *MDT* multidisciplinary tumor board, *WD LPS* well-differentiated liposarcoma

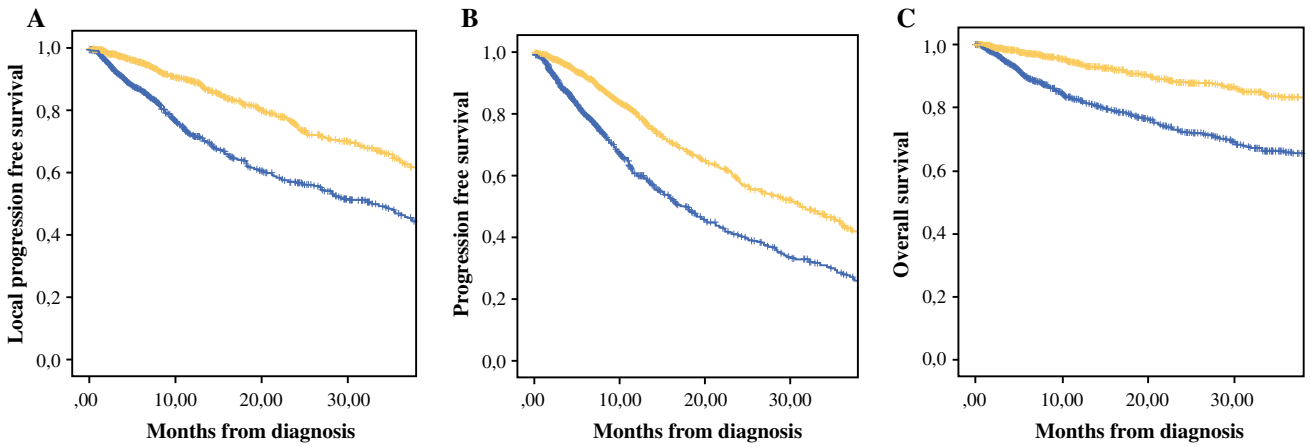

FIG. 1 Local progression-free survival (**a**), progression-free survival (**b**), and overall survival (**c**) of the retroperitoneal sarcoma patients in the NetSarc database. In blue: patients operated on outside of the NetSarc network. In yellow: patients operated on at a NetSarc center. Log-rank $p < 0.0001$ for LRFS, PFS, and OS

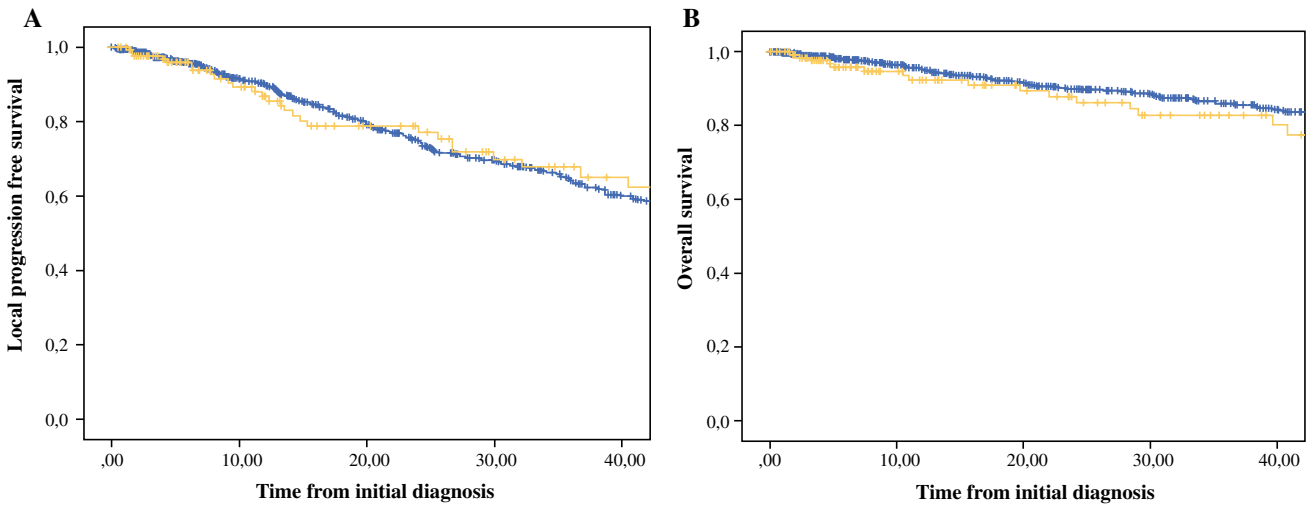

FIG. 2 Local progression-free survival (**a**) and overall survival (**b**) of patients operated on at NetSarc centers. In blue: patients operated on at the 13 NetSarc centers with the largest accrual of RPS patients. In yellow: patients operated on at the 13 NetSarc centers with the smallest accrual of RPS patients. Log-rank $p > 0.05$

with a twofold lower OR of death. This series gathers a nearly exhaustive group of patients with RPS in the nation over this time period, thereby confirming, with a limited risk of bias, the same findings as those from a selection of previous studies that focused on threshold activity. Altogether, these results justify the strategy of centralized management of RPS in reference centers.

Adherence to CPGs was better when the initial RPS surgery was performed in an NSC. This result confirms a recent regional population-based study, which showed that adherence to CPGs for surgery was a strong independent prognostic factor for OS, with an important interaction with management at regional referral centers.[26] The performance of percutaneous preoperative biopsy before surgery was significantly more frequent in NSCs, although it was not performed systematically throughout the network. While a precise analysis of those patients without presurgery biopsy is not feasible in this database, it must be noted that reference centers propose to avoid biopsy when the imaging is characteristic (e.g., heterogeneous dedifferentiated/well-differentiated liposarcoma).[18] From a surgical perspective, the decision concerning the surgical technique and the extent of surgery depends on knowledge of the pathological diagnosis, including the sarcoma histological type. This knowledge translates to better surgical margins in NSCs, with significantly more R0/R1 resections.

This improvement has already been shown using the U.S. National Cancer Database (NCDB).[21,23] In both studies, patients undergoing surgery in an HVC or an academic hospital were more likely to receive R0 resection, although an impact on OS could not be determined.

TABLE 2 Multivariate analysis

	OR	*p*
Local progression-free survival		
Size > 10 cm	1.804	0.000
Grade 2	1.457	0.000
Grade 3	1.765	0.000
LMS	0.462	0.000
First surgery performed in a NSC	0.530	0.000
Progression-free survival		
Size > 10 cm	1.765	0.000
Grade 2	1.384	0.000
Grade 3	2.165	0.000
WDLPS	0.554	0.000
First surgery performed in a NSC	0.604	0.000
Metastatic-relapse-free survival		
Size > 10 cm	1.555	0.003
Grade 1	0.574	0.017
Grade 3	1.822	0.000
WDLPS	0.347	0.000
DDLPS	0.628	0.001
LMS	1.568	0.005
Overall survival		
Size > 10 cm	1.480	0.013
Age at diagnosis	1.014	0.003
Grade 1	0.399	0.004
Grade 3	1.577	0.001
WDLPS	0.414	0.006
LMS	0.619	0.024
First surgery performed in a NSC	0.496	0.000

WD LPS well-differentiated liposarcoma, *DD LPS* dedifferentiated liposarcoma, *LMS* leiomyosarcoma, *MDT* multidisciplinary tumor board, *NSC* NetSarc Center, *OR* odds ratio

Interestingly, assessment by an MDT, which is recommended in various guidelines, was not an independent prognostic factor for OS in our series. However, 29.8% of patients operated on outside of an NSC had an MDT consult at an NSC before surgery. Indeed, surgeons outside NetSarc do not have any specific training in sarcoma, whereas most of the surgeons working within NetSarc have received specific theoretical and practical training on sarcomas, in HVCs and/or during sessions containing live surgery sessions (E-Surge).[17] More recently, a University Degree on sarcomas was created and made mandatory. This finding emphasizes that the decision by a MDT to suggest surgery and send the patient back to a nonspecialized surgeon who asked for advice is not sufficient for optimal technical realization. Importantly, survival was not different between NSCs with the largest number of patients and the other NSCs. These data suggest that the specific sarcoma training of the surgeon is as important as the threshold in case load, with the two factors being complementary. Finally, the definition of sarcoma centers provided by health authorities is a good decision that stimulates specific training.

The question, which also was discussed in a recent editorial, is how to most effectively identify centers to facilitate patient referrals.[27] Should it be based on a threshold that is arbitrarily defined or more authoritatively based on the medical environment and STS cases in general, considering that RPS activity will progress, or should the guideline be based on both factors to satisfy the condition that a sufficient number of centers be retained? In the two series reporting the RPS outcomes of the NCDB according to hospital RPS volume, the threshold was retrospectively defined. In the series by Maurice et al., hospital volume was classified as low volume (< 5) or high volume (≥ 5) based on the average number of RPS cases managed at the hospital per year, with HVCs corresponding to those in the top 10th percentile.[21] The median annual RPS volumes were 19.4 cases for HVHs and 1.0 case for LVHs ($p < 0.001$). However, they did not find a better OS in HVCs with this threshold. In the recent Keung study, the threshold for HVHs was > 10 cases/year.[22] They chose not to use the median number of RPS surgical resections performed per year as a cutoff, because it was only 1.1, which is meaningless. With the > 10 cases/year threshold, only four centers in the United States qualified as HVCs. They demonstrated that 30-day mortality was lower in HVHs than in LVHs and that OS was significantly better and improved with increasing hospital case volume. Conversely, the definition of NSCs was based on the coexistence of sarcoma specialists, as recommended by the European CanCer Organisation (ECCO), and was modeled mostly on the preexisting cancer centers involved in STS cases.[28] Large discrepancies between NSCs were observed. Overall, the OS was significantly better, with a large magnitude of improvement (twofold lower OR for death).

In this series, roughly one-third of patients were operated on at an NSC. These centers are well distributed throughout the territory, which facilitates referrals. However, two-thirds of patients were not, demonstrating the need for referral improvement. During the study period, the proportion of patients operated on at a referral NSC steadily increased from 28 to 44%, suggesting that the official labeling of centers helped increase the accrual of patients in less active centers. In the Keung study, only a minority of patients (9.8%) was treated in the four HVHs, and patients who underwent surgery at LVHs were of lower socioeconomic status.[22] In the Maurice study, the vast majority of HVHs were located in the Northeast United States, while the LVHs were roughly spread equally across the United States.[21] However, improvement in patient

referral also was observed in the United States, although to a lesser extent for RPS surgery than for pancreatic surgery. Indeed, in a study covering 2004 to 2015, the OR of undergoing surgery at an HVH for RPS compared with pancreatic cancer (PC) was 0.65, and a time-trend analysis estimated that the rate of RPS regionalization grew at 30.5% of the rate of PC and remained consistent after using several hospital volume thresholds as continuous variables.[29]

The main limitation of the current study is that details on adjuvant treatments (radiotherapy or chemotherapy) were not registered. However, in France, all these adjuvant treatments are mostly administered in cancer centers, even when the patient is operated on outside of a cancer center, decreasing the possible advantage for HVCs to be linked to multidisciplinary management. However, adjuvant treatment as a whole was not a prognostic factor in our series. Version 2 of the NetSarc database was created in 2016 with the addition of indicators, explaining why some data are missing in this study for a number of patients. Another limitation is that follow-up is far better updated in NetSarc, particularly in HVCs, resulting in fewer events in the other centers or in the LVCs, falsely improving their survival results. This limitation suggests that the difference in survival inside and outside of NetSarc could be even more important.

CONCLUSIONS

These results strongly demonstrate that surgery for primary RPS within reference centers offers the best strategy to improve OS. Designation by health authorities based on ECCO criteria or case load could help to increase patient referrals to designated centers.

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