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ORIGINAL ARTICLE

Improved survival using specialized multidisciplinary board in sarcoma patients

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Background: Sarcomas are rare but aggressive diseases. Specialized multidisciplinary management is not implemented for all patients in most countries. We investigated the impact of a multidisciplinary tumor board (MDTB) presentation before treatment in a nationwide study over 5 years.

Patients and methods: NETSARC (netsarc.org) is a network of 26 reference sarcoma centers with specialized MDTB, funded by the French National Cancer Institute to improve the outcome of sarcoma patients. Since 2010, presentation to an MDTB and second pathological review are mandatory for sarcoma patients in France. Patients' characteristics and follow-up are collected in a database regularly monitored and updated. The management and survival of patients presented to these MDTB before versus after initial treatment were analyzed.

Results: Out of the 12 528 patients aged ≥15 years, with a first diagnosis of soft tissue and visceral sarcoma obtained between 1 January 2010 and 31 December 2014, 5281 (42.2%) and 7247 (57.8%) were presented to the MDTB before and after the initiation of treatment, respectively. The former group had generally worse prognostic characteristics. Presentation to a MDTB before treatment was associated with a better compliance to clinical practice guidelines, for example, biopsy before surgery, imaging, quality of initial surgery, and less reoperations (all $P < 0.001$). Local relapse-free survival and relapse-free survival were significantly better in patients presented to a MDTB before initiation of treatment, both in univariate and multivariate analysis.

Conclusion: The compliance to clinical practice guidelines and relapse-free survival of sarcoma patients are significantly better when the initial treatment is guided by a pre-therapeutic specialized MDTB.

Key words: sarcoma, multidisciplinarity, tumor board, clinical practice guidelines, relapse, survival

Introduction

Soft tissue and visceral sarcomas (STS) constitute a heterogeneous group of rare connective tissue cancers, in terms of histology, molecular biology, and clinical presentations, and an estimated incidence of 5.6–5.9/100 000 per year [1–4]. Because of their rarity, STS are often initially misrecognized, misdiagnosed, and as a consequence not treated according to clinical practice guidelines (CPG) [5–7]. Inadequate diagnostic procedures and treatment, for instance, 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 [4–8].

However, optimal surgical removal of sarcoma, with *en bloc* resection, is the mainstay of the curative treatment of localized STS [4–8]. The quality of initial surgery is a major prognostic factor for recurrence-free survival and overall survival in all series [9–12]. In all CPGs, it is recommended that the management of sarcoma patients should be carried out by a dedicated multidisciplinary team, including expert pathologists, radiologist, surgeons, radiation oncologist and medical oncologists treating a large number of patients. In most countries, the diagnosis and treatment of patients with sarcoma can be carried out in any oncology facility. Conversely, in some countries (e.g. Scandinavian countries, UK), the management of sarcoma patients must be carried out in dedicated reference centers [6–8, 13]. Most CPG recommended that patients with a suspected diagnosis of STS should be referred at a sarcoma center before any treatment [6–8].

The French National Cancer Institute (INCa), validated and supported the creation of a clinical network for sarcoma (NetSarc) in 2009, which was missioned to improve the management and outcome of sarcoma patients. Twenty-six reference centers were identified in this clinical network. Netsarc is linked to a sarcoma pathological reference network (RRePS 'Network for expert pathology diagnosis in sarcoma'), of 23 reference centers for sarcoma pathology in charge of the second histological review of each suspected case of sarcoma. A common database (netsarc.org) gathering all cases of histologically reviewed sarcoma presented in multidisciplinary tumor boards (MDTB) was created and implemented, describing the diagnostic, therapeutic management, and the clinical outcome in terms of relapse and survival.

As of 8 December 2016, this database included 37 833 sarcoma patients, with 12 528 patients aged >15 years enrolled between 1 January 2010 and 31 December 2014. The aim of the present study is to evaluate the impact of the presentation of the patients with soft tissue or visceral sarcoma to a specialized MDTB before the initial treatment.

Patients and methods

The network

Each Netsarc center proposes a MDTB board gathering at minimum sarcoma specialized, pathologist(s), radiologist(s), surgeon(s), radiation oncologist(s), medical oncologist(s), and often molecular biologist(s), orthopedist(s), pediatrician(s). All sarcoma patient cases, discussed in MDTB within NetSarc centers were recorded in the database, by a dedicated team of Clinical research assistant (CRAs), supervised by three Coordinating centers (Centre Leon Berard, Gustave Roussy, Institut Bergonié). Patient files may be presented by the primary care physician at any step: 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. Monitoring of the centers is carried out by the three coordinating centers on a regular basis.

The NETSARC database

The objectives of NETSARC are as follows: (i) to obtain an exhaustive description of 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. The center which carried out the first resection is documented. The surgical resection system (R) from the Union International Centre le cancer (UICC) was chosen to define the quality of surgery. This system distinguishes the quality of resection (R), using the surgical and pathological report: R0 = macroscopically complete *en bloc* resection with *in sano* resection margins, R1 = same, but with tumor cells visible on resection margins, and R2 = macroscopic residual disease. 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 non-missing observations. The statistical test used for comparison was a chi-square (or a Fisher's exact) 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 (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. Relapse-free survival (RFS) is computed from the date of diagnosis to the date of the last follow-up or the date of the first metastasis. Survival curves were plotted using a Kaplan–Meier method. Survival was compared using the log-rank test. Univariate and multivariate analyses for LRFS and RFS included the following: (i) classical prognostic factors for sarcoma, and (ii) variables differing across the two groups (MDTB before versus after treatment) which had a prognostic impact on LRFS, RFS, or OS. These included gender, age, grade [14], sarcoma size, site, depth, presentation at the MDTB before versus after initiation of treatment. Cox proportional hazard 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 one error ($P \geq 0.05$). All statistical tests were two-sided. All statistical analyses were carried out using SPSS (version 19.0).

Results

Patient population

As of 8 December 2016, 37 833 patients were prospectively included in the Netsarc database. The patient population studied

here is that of patients aged 15 years and above, with an histologically reviewed and confirmed soft tissue or visceral sarcoma, diagnosed in France from 1 January 2010 to 31 December 2014, in any anatomic site. Bone sarcomas and desmoid tumors were not included. About 12 528 patients match these criteria and are included in this analysis (Table 1).

Patient characteristics

We compared the characteristics of patients presented in a Netsarc MDTB prior ($N = 5281$, 42.2%) or after ($N = 7247$, 57.8%) the primary treatment (Table 2). The proportion of patients presented to 1 of the 26 Netsarc MDTB before initiation of treatment increased from 38.9% to 45.7% ($P < 0.001$) between 2010 and 2014. Overall, the characteristics of patients presented to a NETSARC MDTB before treatment were less favorable, with a higher proportion of patients with metastasis at diagnosis and with deep seated sarcomas, larger tumors, of worse grade (all $P < 0.001$, see Table 2). Locations were also significantly different, with less visceral sarcomas in patients referred to MDTB before the initiation of first treatment, more retroperitoneal sarcomas, but less head and neck sarcomas ($P < 0.001$ for all sites, Table 2)

Table 1. Description of the patient population

Characteristics	Incident patients $N = 12\,528$
Gender	
Male	6207 (49.6%)
Female	6321 (51.1%)
Age at first diagnosis	
Median (min–max)	61 (18–101)
Type of tumor	
Soft tissue	9604 (76.7%)
Visceral	2924 (23.3%)
Site	
Head and neck	860 (6.9%)
Trunk	6791 (54.2%)
Retroperitoneum	1225 (9.8%)
Trunk wall	1396 (11.1%)
Upper limb	1126 (8.9%)
Lower limb	3751 (29.9%)
Size of the tumor	
Median (min–max)	96 (1–940)
Histology	
Leiomyosarcoma	1617 (12.9%)
GIST	1103 (8.8%)
Dediff liposarcoma (LPS)	987 (7.9%)
Well diff. LPS	906 (7.2%)
Myxoid LPS	347 (2.8)
UPS	890 (7.1%)
Myxofibrosarcoma	561 (4.5%)
Other > 100 cases	4576 (36.5%)
Other < 100 cases	1541 (12.3%)
Grade	
1	1802 (14.5%)
2	2544 (20.3%)
3	3546 (28.3%)
Unknown	2945 (23.5%)
Non-applicable	1691 (13.5%)
Metastases at diagnosis	
Yes	1594 (12.7%)
No	9646 (77.0%)
Unknown	1288 (10.2%)
No of pts managed by NETSARC center	
Median (min–max)	234 (44–1351)

Diagnostic before treatment

Clinical practice guidelines recommend that imaging and biopsy should be carried out before any therapeutic approach in sarcoma [6–8]. A higher number of patients presented to a Netsarc MDTB before treatment had adequate imaging of the tumor before treatment (Table 3). Similarly, a higher proportion of patients presented to a MDTB before surgery had biopsy before surgery: only 41% of the patients treated before presentation to a NetSARC MDTB had a biopsy versus 85.7% in patients presented to a MDT (Table 2).

Quality of surgical resection

We then focused on the 8844 patients with a documented absence of metastasis and in whom surgery was mentioned in the database. As expected, a higher proportion of patients presented to MDTB after treatment had reported surgery, since this was a selection criteria ('treatment before') for this group. The quality of the primary surgery carried out after versus before presentation to the Netsarc MDTB was superior with significantly more R0 resections, less R2 resections, and less resections non-evaluable for this parameter (Table 2) ($P < 0.001$). About 1065 (17.4%) patients had secondary resection when treatment was carried out before NetSarc MDTB versus 165 (6.0%) in those where treatment was given after MDTB ($P < 0.001$). After this secondary resection, the quality of the final surgery remained better for patients presented to a MDTB before versus after surgery with significantly more R0 resections and less R2 resections. Reoperation do not compensate for the inadequate initial patient management ($P < 0.001$) (Table 2).

Survival

We analyzed here the population of 9646 patients without diagnosed metastasis at initial diagnosis. With a median follow-up of 26 months, the LRFS of patients treated before presentation to a MDTB was significantly worse than that of the remaining patients, with a 2-year LRFS of 65.4%, versus 76.9% in these two groups, respectively (Figure 1A, $P < 0.001$). RFS was also significantly worse for patients treated before presentation to a MDTB than for those presented before, with a 2-year LRFS of 46.6%, versus 51.7% in each groups (Figure 1B, $P < 0.001$). Multivariate analysis in non-metastatic patients included the parameters differing between the two groups (MDTB before versus after treatment), with prognostic value for LRFS and RFS (gender, age, size, tumor site, grade, depth, presentation to a MDTB before treatment). The latter was associated with the highest risk ratio for LRFS and was also a strong independent negative prognostic factor for RFS (Table 3). Overall survival was too early to assess given the median follow-up (not shown).

Table 2. Patients' characteristics, procedures, and NETSARC MDTB

Patient characteristics	NETSARC MDTB before treatment		*P* value
	Yes (*N* = 5281)	No (*N* = 7247)	
Gender			
Female	2507 (47.5%)	3814 (52.6%)	
Male	2774 (52.5%)	3433 (47.4%)	
Tumor size (mean, SE)	109.6 (80.6)	85.6 (75.4)	<0.001
Site			
Soft tissue	4492 (85.1%)	5112 (70.5)	<0.001
Visceral	789 (14.9%)	2135 (29.5%)	
Deep seated			
No	671 (12.7%)	1574 (21.7%)	<0.001
Yes	4449 (84.2%)	5377 (74.2%)	
Unknown	161 (3.0%)	314 (4.1%)	
Grade			
1	716 (13.6%)	1086 (15.0%)	<0.001
2	1058 (20.0%)	1486 (20.5%)	
3	1463 (27.7%)	2083 (28.7%)	
Unknown	1345 (25.4%)	1600 (22.1%)	
NA	699 (13.2%)	992 (13.6%)	
Metastasis at diagnosis			
Yes	832 (15.8%)	762 (10.5%)	<0.001
No	3904 (73.9%)	5742 (79.2%)	
Unknown	545 (10.3%)	743 (10.3%)	
Diagnostic procedures			
Imaging of the primary tumor			
Yes	4642 (87.9%)	4375 (60.4%)	<0.001
No	171 (3.2%)	623 (8.6%)	
Unknown	468 (8.9%)	2249 (31.0%)	
Diagnostic biopsy			
Yes	4633 (87.7%)	3036 (41.9%)	<0.001
No	481 (9.1%)	3315 (45.7%)	
Unknown	167 (3.2%)	896 (12.4%)	
Therapeutic procedure[a]			
Quality of first surgery[b]			
R0	1436 (52.6%)	1968 (32.2%)	<0.001
R1	845 (30.9%)	1965 (32.1%)	
R2	204 (7.1%)	1148 (18.8%)	
NE	246 (9.1%)	1032 (16.9%)	
Reexcision after first surgery			
Yes	165 (6.0%)	1065 (17.4%)	<0.001
No	2320 (85.0%)	4916 (65.7%)	
NE	246 (9.1%)	1032 (16.9%)	
Quality of final surgery[b]			
R0	1571 (57.5%)	2845 (46.5%)	<0.001
R1	773 (28.3%)	1529 (25.0%)	
R2	141 (5.1%)	707 (11.5%)	
NE	246 (9.1%)	1032 (16.9%)	

[a]Missing data in 3684 patients who had not been operated at the time of the analysis. Only non-metastatic patients in whom surgery was documented are described; these are 8844 patients, in whom MDTB was before treatment (*N* = 2731), or after treatment (*N* = 6113).
[b]Quality of resection (R) is classified as: R0 = macroscopically complete *en bloc* resection with *in sano* resection margins, R1 = same, but with tumor cells visible on resection margins, R2 = macroscopic residual disease.

Table 3. Multivariate analysis of prognostic factors for survival

	Beta	E.S.	HR	*P* value
Local relapse-free survival				
MDTB after treatment	0.590	0.071	1.804	0.000
Grade 3	0.272	0.064	1.312	0.000
Age	0.007	0.002	1.007	0.000
Tumor size	0.002	0.000	1.002	0.000
Internal trunk	−0.353	0.081	0.703	0.000
Limb site	0.343	0.079	0.710	0.000
Grade NA	−0.340	0.114	0.712	0.003
Grade 1	0.377	0.096	0.686	0.000
Relapse-free survival				
Grade 3	0.634	0.072	1.886	0.000
MDT after treatment	0.234	0.052	1.263	0.000
Age	0.005	0.001	1.005	0.001
Tumor size	0.002	0.000	1.002	0.000
Limb site	−0.289	0.065	0.749	0.000
Grade NA	−0.317	0.106	0.728	0.003
Internal trunk	−0.151	0.068	0.860	0.025
Grade 1	−0.482	0.096	0.618	0.000

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 one error ($P \geq 0.05$).
Grade NA, not applicable.

Discussion

Sarcomas are rare cancers for which multidisciplinary management in a reference center is recommended in all CPG [6–8]. Most sarcoma patients are however not managed in reference centers, worldwide. The impact of a management without the support of a specialized multidisciplinary team on relapse and survival of sarcoma patients is not precisely known.

The question addressed in this work was whether a multidisciplinary assessment conducted by a dedicated multidisciplinary sarcoma team, a 'MDTB' before the therapeutic procedure influences patient management and outcome. The general conclusion is that presentation of the patient to an MDTB before any treatment procedure is associated with a better compliance to the CPG, a better quality of surgery, a better RFS, with significantly less reoperation. Its impact on long-term outcome, survival, will need to be assessed with a longer follow-up.

Netsarc is a nationwide project aiming to improve the management and outcome of sarcoma patients. In order to be able to measure and report the outcome of sarcoma patients, the Netsarc database collected prospectively patient and tumor related information since 1 January 2010 from the 26 reference centers. This article reports an analysis of *only* incident patients with sarcoma aged ≥15 years with an initial diagnosis from 1 January 2010 to 31 December 2014. In view of the incidence of sarcomas, the expected number of incident case of sarcoma was close to 3900 per year in France; for soft tissue and visceral sarcoma of patients aged over 15 years (4.9/100 000 per year), it was close to 3070 per year. Overall, in this 5-year period, 15 350 incident cases of sarcomas were thus expected. The 12 528 patients matching these criteria identified in the Netsarc database represent 81.6% of this theoretical incidence, and therefore a large fraction of the incident population of sarcoma patient in this country.

This population of patients is a real life population: 12% of patients have metastasis; elderly patients >80 ($n = 1474$, 11.8%) and 90 ($n = 107$, 0.8%) also represent a significant proportion of this population usually not captured in clinical trials. Although the database aimed to be exhaustive, clinical and tumor parameters were not available for all patients; for example, unknown grade (23%) or unknown metastatic static status (10%). Information was lacking both in reference and non-reference centers, and this is an obvious objective of improvement for this project.

Patients whose files were discussed in a MDTB before treatment had worse prognosis features: more male patients, larger tumors, of higher grade, and more frequently metastatic. This suggests that primary care physicians may refer earlier sarcoma patient with bad prognostic features to the reference centers. Patients presented to a MDTB before treatment were managed more frequently in compliance with clinical practice guidelines. The difference was very significant for the imaging of the primary tumor, which was not done or unknown in 12% versus 40%, respectively for patients presented to MDTB before versus after treatment. In the former group, the percentage of patients without documented imaging remains too high (3% not done, and 8% unknown). But it must also be noted that not all patients presented in a MDTB before treatment were subsequently managed by the reference center: 17% of these patients were operated outside a reference center (not shown). This is also an important target for improvement.

The lack of compliance to the clinical practice guidelines was particularly impressive for the rate of pretreatment biopsy of the primary tumor in patients presented to the MDTB before versus after initiation of treatment (87% versus 41%). Optimal surgery of sarcoma can only be carried out with a proper knowledge of the diagnosis and extension and the tumor, as clearly stated in the CPG [6–12, 15]. This is lacking in over 50% of the patient not presented in a MDTB before treatment. As a consequence, the rate of optimal R0 surgery was very significantly lower in this group of patients (32% versus 52%), and conversely a very high rate of incomplete (R2 or unknown) surgery was observed in this group 36% versus 16%. It is well documented that R2 surgery exposes the patient to a major risk of local and distant relapse and death, while R0 surgery is associated with the best overall survival [16–18].

Significantly more patients had thus to be re-operated in the group not presented to a MDTB (17% versus 6%) exposing the patient to a higher cost and morbidity of the total treatment procedure [19, 20]. Of note, despite reoperation, the final results in terms of quality of surgery (R0, R1, and R2) remained significantly worse in the group of patient not presented to an MDTB before treatment. The 24-month overall survival of patients with final R2 or non-evaluable resection is 78.4% only, versus 92.4% for R0 and 88.5% for R1 resected patients (not shown) pointing to a major impact of these inadequate procedures on survival. Importantly also the outcome of this nationwide population of

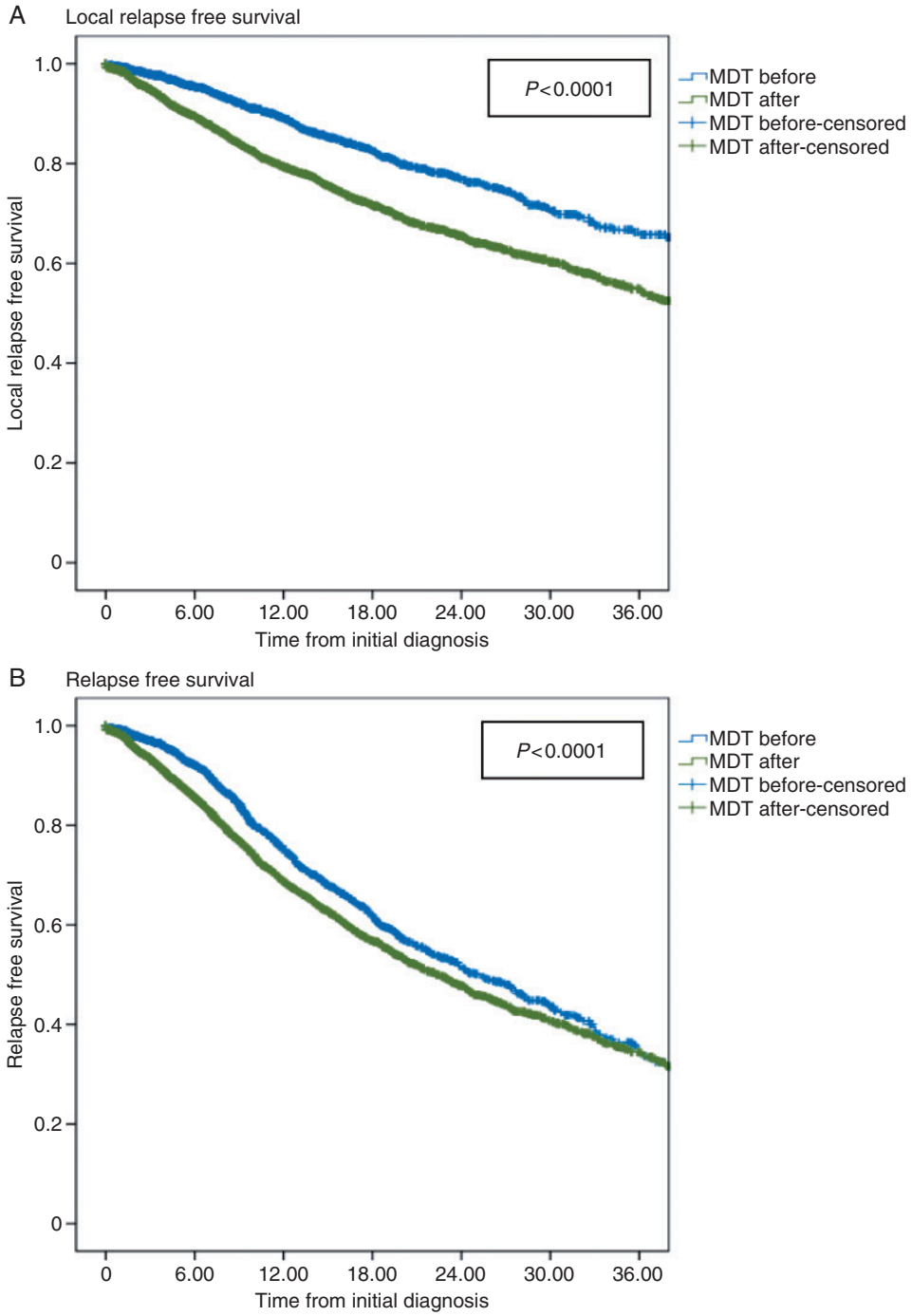

Figure 1. Local relapse-free survival and relapse-free survival in non-metastatic sarcoma patients according to the date of MDTB presentation. (A) Local relapse-free survival in patients presented to a MDTB before, versus after initiation of treatment. (B) Relapse-free survival in patients presented to a MDTB before, versus after initiation of treatment.

patients is worse than that reported in prospective series published from reference centers, probably because of less selections biases on age, performance status, or comorbidities, consistently with a previous smaller series [21, 22].

The impact on overall survival of the whole population is too early to be evaluated but lack of presentation to an MDTB will likely have a negative impact on overall survival. Obviously, this analysis will need to be reassessed with a longer follow-up. Finally, in multivariate analysis, presentation to a MDTB was identified as one of the strongest negative predictive factor for LRFS and RFS, in addition to the classical prognostic factors such as patients' age, tumor size, grade, depth, and site, confirming the importance of this parameter for patient outcome.

Our series has several limitations. Obviously, this was not a prospective randomized study assessing the impact of MDTB, which would be technically difficult to organize in practice. In addition, an even more exhaustive coverage of the incident sarcoma patient population and of all parameters related to the

tumor is required. The description of postoperative treatment is limited, while it may influence also survival in large series [23]. Importantly, an evaluation beyond a single nation will also be important to confirm these findings. This may become possible through the recently launched European Reference Network for Rare Cancers EURACAN (euracan.com), for sarcomas as well as other rare cancers.

Nevertheless, this nationwide series provides a tangible confirmation in a very large unselected nationwide population of the statements proposed in clinical practice guidelines 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 [23–25]. The mechanisms of their worse prognosis are better understood in view of the present results. Given the magnitude of improvement of RFS observed when sarcoma patient files are discussed before treatment, these results strongly suggests that organizing patient management within reference centers offers the best option to improve the outcome of sarcoma patients.

In conclusion, these results show that the management of patients with sarcomas must be carried out under the supervision of a multidisciplinary team with experience as early as in the diagnostic phase, before any treatment is initiated. When this is not carried out, clinical practice guidelines are more often not followed, and risk of relapse and reoperation increase, with an increased rate of reoperation and cost for the patient.

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Appendix

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