Ann Surg Oncol (2019) 26:3526–3534
https://doi.org/10.1245/s10434-019-07494-6

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – SARCOMA

Watch and Wait Approach for Re-excision After Unplanned Yet Macroscopically Complete Excision of Extremity and Superficial Truncal Soft Tissue Sarcoma is Safe and Does Not Affect Metastatic Risk or Amputation Rate

Gauthier Decanter, MD[1,2], Eberhard Stoeckle, MD[3], Charles Honore, MD, PhD[4], Pierre Meeus, MD[5], Jean Camille Mattei, MD, PhD[6], Pascale Dubray-Longeras, MD[7], Gwenael Ferron, MD[8], Sébastien Carrere, MD[9], Sylvain Causeret, MD[10], Jean-Marc Guilloit, MD[11], Magali Fau, MD[12], Philippe Rosset, MD, PhD[13], Jean-Christophe Machiavello, MD[14], Jean Baptiste Delhorme, MD, PhD[15], Nicolas Regenet, MD[16], François Gouin, MD, PhD[17], Jean-Yves Blay, MD, PhD[18], Jean-Michel Coindre, MD, PhD[19], Nicolas Penel, MD, PhD[20], and Sylvie Bonvalot, MD, PhD[21]

[1]Department of Medical Oncology, Oscar Lambret Center, Lille, France; [2]General Oncology Department, Oscar Lambret Cancer Center, Lille, France; [3]Department of Surgery, Bergonie Institute, Bordeaux, France; [4]Department of Surgical Oncology, Gustave Roussy Cancer Campus, Villejuif, France; [5]Department of Surgical Oncology, Centre Léon Bérard, Lyon, France; [6]Department of Orthopedic Surgery, Hôpital Nord, Marseille, France; [7]Department of Medical Oncology, Centre Jean Perrin, Clermont-Ferrand, France; [8]Department of Surgical Oncology, Institut Universitaire du Cancer de Toulouse – Oncopole, Toulouse, France; [9]Department of Surgical Oncology, Montpellier Cancer Centre, Montpellier, France; [10]Department of Surgery, Centre Georges François Leclerc, Dijon, France; [11]Department of Medical Oncology, Regional Cancer Centre, Caen, France; [12]Department of Medical Surgery, Centre Alexis Vautrin, Vandœuvre-lès-Nancy, France; [13]Department of Orthopedic Surgery, University Hospital of Tours, Tours, France; [14]Breast Cancer and Reconstructive Surgery Unit, Centre Antoine Lacassagne, Nice, France; [15]Department of General and Digestive Surgery, Hautepierre Hospital, Strasbourg University Hospital, Strasbourg, France; [16]Department of Digestive Surgery, Nantes Hospital, Nantes, France; [17]Department of Orthopedic Surgery, Leon Berard Center, Lyon, France; [18]Department of Medical Oncology, Leon Berard Center, Lyon, France; [19]Department of Pathology, Bergonié Cancer Institute, Bordeaux, France; [20]Medical Oncology Department, Centre Oscar Lambret and Lille University Hospital, Lille, France; [21]Department of Medical Oncology and Surgery, Gustave Roussy Institute, Villejuif, France

ABSTRACT

Background. The benefits of systematic re-excision (RE) after initial unplanned excision (UE) of soft tissue sarcoma (STS) are unknown.

Objective. The aim of this study was to evaluate the impact of delayed RE versus systematic RE after UE on overall survival (OS), metastatic relapse-free survival (MRFS), local relapse-free survival (LRFS), and rate of amputation.

Methods. Patients who underwent complete UE, without metastasis or residual disease, for primary extremity or superficial STS between 2007 and 2013 were analyzed. The amputation rate, LRFS, MRFS, and OS were assessed in cases of systematic RE in sarcoma referral centers (Group A), systematic RE outside of community centers (Group B), or without RE (Group C).

Results. Groups A, B, and C included 300 (48.2%), 71 (11.4%), and 251 (40.4%) patients, respectively. Median follow-up was 61 months and 5-year OS was 88.4%, 87.3%, and 88% in Groups A, B, and C, respectively ($p = 0.22$), while 5-year MFRS was 85.4%, 86.2%, and 84.9%, respectively ($p = 0.938$); RE ($p = 0.55$) did not influence MRFS. The 5-year LRFS was 83%, 73.5%, and 63.8% in Groups A, B and C, respectively ($p = 0.00001$). Of the 123 local recurrences observed, 0/28, 1/15, and 5/80

First Received: 18 January 2019;
Published Online: 23 July 2019

G. Decanter, MD
e-mail: g-decanter@o-lambret.fr

patients in Groups A, B, and C, respectively, required amputation ($p = 0.41$). Factors influencing LRFS were adjuvant radiotherapy [hazard ratio (HR) 0.21; $p = 0.0001$], initial R0 resection (HR 0.24, $p = 0.0001$), and Group A (HR 0.44; $p = 0.01$).

Conclusion. Systematic RE in sarcoma centers offers best local control but does not impact OS. Delayed RE at the time of local relapse, if any, could be an option.

Localized adult extremity soft tissue sarcoma (STS) is a therapeutic challenge, ideally requiring wide en bloc resection associated with (neo)adjuvant radiotherapy in selected high-grade tumors[1,2] after appropriate diagnostic work-up[3] and early multidisciplinary tumor board discussion.[4] Adjuvant or neoadjuvant chemotherapy is an option that is still debated;[5–8] however, despite this optimal treatment, 20–30% of patients will relapse with distant metastasis and 10% will experience a local relapse (LR).[9–13] The major predictor for LR is tumor-free surgical margins (R0 resection).[14,15] Initial management in sarcoma referral centers (SRCs) is associated with a significantly better outcome.[16]

Unfortunately, unplanned excision (UE) remains a common diagnostic circumstance for STS, affecting an estimated 18–66% of cases,[10,16–20] and leads to a higher risk of residual disease and LR. Indeed, residual disease is found in approximately 50% of specimens after systematic re-excision (RE),[9,21–24] which justifies the systematic policy recommended in the guidelines, when feasible.[3,25] Patients with RE achieve comparable overall survival (OS) as those optimally operated from the beginning.[5,6,9,10,17,20,26,27] This strategy is justified when macroscopic residual tumor is observed or when surgical or pathological reports identify piecemeal resection. However, when en bloc marginal excision has been performed, the benefit of a systematic immediate RE is questionable. RE often requires a larger excision that could have been performed in a less extensive approach from the beginning, and can sometimes be mutilating, necessitating additional techniques. Final pathology reports often conclude to the absence of residual cells identified in the re-excised specimen. After en bloc marginal excision, some patients will not recur and the impact of an LR on metastatic risk is unclear. An alternative policy is to perform RE when an LR occurs, if any.

The objective of this retrospective study was to evaluate the impact of a 'watch and wait' approach after UE of extremity or superficial truncal STS without any macroscopic residual disease or piecemeal resection on local relapse-free survival (LRFS), metastatic relapse-free survival (MRFS), OS, and rate of amputation.

PATIENTS AND METHODS

Patient Selection

From the ConticaBase prospective database, all consecutive patients with STS arising in the limbs or superficial truncal initially operated outside of community centers and then referred to 1 of 18 participating SRCs in France between 1 January 2007 and 31 December 2013 were included. Cases corresponding to open surgical biopsies, R2 or piecemeal resections, and patients definitively judged non-amenable to curative-intent surgery (e.g. multifocal disease, presence of node involvement, or presence of distant metastasis) were excluded. All cases were confirmed by pathological review by a panel of experts from the French Sarcoma Group.

R2 resection was qualified according to operative reports indicating macroscopic residual disease, postoperative imaging, or clinical examination, whereas piecemeal resection was qualified according to operative or pathological reports (indicating more than one specimen).

Description of the Collected Parameters

The following data were extracted from the database: (1) tumor characteristics [size, macroscopic involvement of muscle, skin, or nerve/vessels, primary location, depth, National Federation of French Cancer Centres (FNCLCC) grade, and presence of multifocal pattern]; (2) patient characteristics (sex, age, underlying genetic condition, and prior history of cancer); (3) management characteristics (surgery performed, RE in SRCs or outside of community centers, margins after RE (R0, R1), and administration of (neo)adjuvant radiotherapy or chemotherapy); and (4) outcome (local or distant relapse and status at last-follow-up). Surgical margins (R0 vs. R1) were assessed during the first surgical procedure; however, a second opinion on surgical margins was not retrospectively feasible. Surgical margins after RE were not assessed because standardization was not possible.

Patients referred without macroscopic residual disease or piecemeal resection were grouped into three groups:

(1) *Group A* Patients who underwent systematic RE in SRCs after referral.
(2) *Group B* Patients who underwent RE outside of community centers, which had already been performed at referral.
(3) *Group C* Patients without systematic RE, grouping together patients who could have had RE but did not undergo surgery intentionally and patients for whom radiotherapy was chosen over surgery due to the potential morbidity of RE.

TABLE 1 Patient characteristics

Categories	Re-excision in sarcoma referral centers (Group A) (n = 300)	Re-excision outside of community centers (Group B) (n = 71)	Absence of scar re-excision (Group C) (n = 251)	Total	p value
Female	128 (42.7)	41 (57.7)	125 (49.8)	284 (47.3)	0.042
Male	172 (57.3)	30 (42.3)	126 (50.2)	328 (52.7)	
No genetic condition	291 (98.6)	69 (98.6)	245 (98.9)	605 (98.7)	0.984
Genetic condition	4 (1.4)	1 (1.4)	3 (1.2)	8 (1.3)	
No prior cancer	256 (86.8)	64 (91.4)	228 (91.9)	548 (89.4)	0.127
Prior cancer	39 (13.2)	6 (8.6)	20 (8.1)	65 (10.6)	
Age $\leq$ 58 years	157 (52.3)	28 (39.4)	130 (51.8)	315 (50.6)	0.132
Age $>$ 58 years	143 (47.7)	43 (60.6)	121 (48.2)	307 (49.4)	
Lower limb primaries	156 (52.0)	37 (52.1)	126 (50.2)	319 (51.2)	0.577
Truncal primaries	69 (23.0)	12 (16.9)	64 (25.5)	145 (23.3)	
Upper limb primaries	75 (25.0)	22 (31.0)	61 (24.3)	158 (25.4)	
No muscle involvement	218 (72.7)	55 (77.5)	160 (63.7)	433 (69.6)	0.024
Muscle involvement	82 (27.3)	16 (22.5)	91 (36.3)	189 (30.4)	
No neurovascular involvement	295 (98.3)	68 (95.8)	246 (98.0)	609 (97.9)	0.395
Neurovascular involvement	5 (1.7)	3 (4.2)	5 (2.0)	13 (2.1)	
Tumor size $\leq$ 50 mm	178 (60.5)	47 (68.1)	116 (47.2)	341 (56.0)	0.001
Tumor size $>$ 50 mm	116 (39.5)	22 (31.9)	130 (53.8)	268 (44.0)	
Superficial tumor	118 (48.2)	34 (52.3)	74 (32.5)	226 (42.0)	0.001
Deep tumor	127 (51.8)	31 (47.7)	154 (67.5)	312 (58.0)	
Liposarcoma	47 (15.7)	12 (16.9)	55 (21.9)	114 (18.3)	0.045
Leiomyosarcoma	65 (21.7)	14 (19.7)	30 (12.0)	109 (17.5)	
Myxofibrosarcoma	75 (25.0)	18 (25.4)	50 (19.9)	143 (23.0)	
Synovial sarcoma	18 (6.0)	6 (8.5)	17 (6.8)	41 (6.6)	
Other sarcomas	95 (31.7)	21 (19.6)	99 (39.4)	215 (34.5)	
Unifocal pattern	278 (93.8)	69 (97.2)	228 (91.6)	575 (93.3)	0.211
Multifocal pattern	18 (6.1)	2 (2.8)	21 (8.4)	41 (6.7)	
Grade 1	56 (19.3)	14 (20.3)	48 (20.3)	118 (19.8)	0.505
Grade 2	111 (38.3)	33 (47.8)	100 (42.2)	244 (40.9)	
Grade 3	123 (42.4)	22 (31.9)	89 (37.6)	234 (39.3)	
R1 resection after first procedure	40 (13.3)	7 (9.9)	121 (57.8)	168 (27.0)	0.0001
R0 resection after first procedure	231 (77.0)	58 (81.7)	106 (42.2)	395 (63.4)	
No (neo)adjuvant chemotherapy	247 (82.9)	67 (94.4)	235 (94.0)	549 (88.7)	0.0001
Adjuvant chemotherapy	51 (17.1)	4 (5.6)	15 (6.0)	70 (11.3)	

TABLE 1 continued

Categories	Re-excision in sarcoma referral centers (Group A) (n = 300)	Re-excision outside of community centers (Group B) (n = 71)	Absence of scar re-excision (Group C) (n = 251)	Total	p value
No (neo)adjuvant radiotherapy	107 (35.9)	32 (45.1)	128 (51.4)	267 (43.2)	0.001
Adjuvant radiotherapy	191 (64.1)	39 (54.9)	121 (48.6)	351 (56.8)	

Data are expressed as n (%)

Database and Ethical Considerations

The ConticaBase is shared via the internet and the technical aspects are described at www.conticabase.org (charter/technical description). It is an anonymized and encrypted database with defined and controlled access rights that have been approved by the French Ethics Committee and Agency in charge of non-interventional trials—Comité consultatif sur le traitement de l'information en matière de recherche dans le domaine de la Santé (CCTIRS: approval number 09.594; date of approval 24 November 2009) and Commission Nationale Informatique et Liberté (CNIL: approval number 909510; date of approval 5 February 2010).

Statistical Analysis

The objectives of the present analysis were to analyze LRFS, MRFS, and OS according to the three strategies, using univariate ('crude' or 'unadjusted') analysis and adjusted analysis with confounding factors taken into account. We used classical descriptive statistics of median and maximum/minimum values for continuous data and numbers and percentages for categorical data.

Survival analyses were conducted in compliance with DATECAN recommendations.[28] OS was calculated from the date of diagnosis until the death date, regardless of cause, or until the date of last follow-up (censored data). LRFS was calculated from the date of diagnosis until the date of LR or the date of last follow-up/death (censored data). MRFS was calculated from the date of diagnosis until the date of metastasis diagnosis, the date of death, regardless of cause, or the date of last follow-up (censored data).

In univariate analysis, prognostic factors were identified using the univariate Cox model for continuous parameters and the log-rank test for categorical parameters.

The characteristics of Group A patients differed widely from the other patients, and confounding factors that could bias the impact of RE were identified. These were defined as factors that were associated with both RE in SRCs and outcome (LRFS or MFRS). After indentifying confounders, these confounders were used in the multivariate Cox analysis.

RESULTS

Study Population and Characteristics

A total of 1037 patients with UE were registered in the ConticaBase between January 2007 and December 2013, of whom 622 met the selection criteria; Groups A, B, and C accounted for 300 (48.2%), 71 (11.4%), and 251 patients (40.4%), respectively.

Baseline characteristics are described in Table 1. There were some differences in baseline characteristics among the three groups. Group A patients were mostly treated by combined treatment, i.e. chemotherapy and/or radiotherapy; Group B patients were more frequently women; and Group C patients had more muscle involvement, deep tumors and tumors over 50 mm in size, and fewer R0 resections (determined by a non-expert pathologist).

Overall, 351 patients (56.4%) received adjuvant radiotherapy. Radiotherapy was more frequently administered in Group A compared with Groups B and C, i.e. 191 (64.1%), 39 (54.9%), and 121 (48.6%), respectively (p = 0.0021). In all three groups, radiotherapy was more frequently used in cases with large tumor, deep location, and muscle involvement. Among those patients receiving radiotherapy, 74% presented with at least one of these characteristics, compared with 56.4% among those who did not have radiotherapy ($p < 0.0001$).

Survival Analysis

The median follow-up was 61 months (range 1–125). During follow-up, 123 LRs, 36 metastatic relapses, and 23 deaths occurred.

The 5-year OS rate was 88.4% ± 1.8%, 87.3% ± 4.5%, and 88.0% ± 5.1% in Groups A, B, and C, respectively

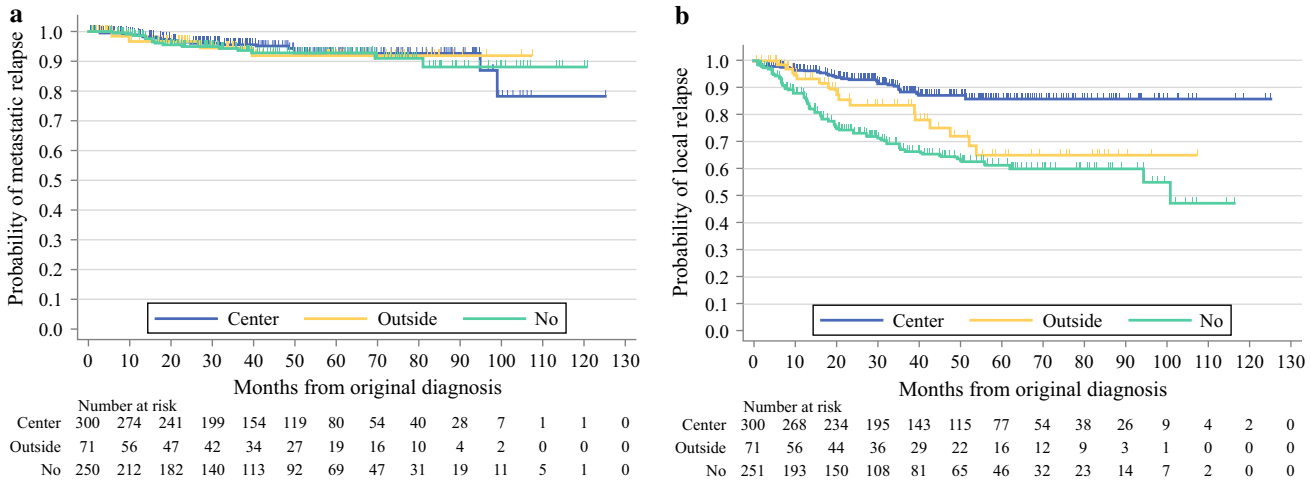

FIG. 1 **a** Metastatic and **b** local relapse-free survival for patients in Groups A, B, and C

(p = 0.228). Similarly, the 5-year MFRS rate was 85.4% ± 2.3%, 86.2% ± 4.1%, and 84.9% ± 4.2% in Groups A, B, and C, respectively (p = 0.938) (Fig. 1a).

In the univariate analysis, RE in SRCs significantly impacted LRFS; the 5-year LRFS rate was 83.0% ± 2.5%, 73.5% ± 6.1%, and 63.8% ± 4.4% in Groups A, B, and C, respectively (p = 0.00001) (Fig. 1b). LRFS was significantly better in Group A compared with Groups B and C [crude hazard ratio 0.43, 95% confidence interval (CI) 0.23–0.80; p = 0.00001].

Identification of Confounders

Table 1 shows factors not balanced between the three groups. After RE, the R0 resection rate was higher in Group A compared with Group B. Among the parameters, two were associated with LRFS and were regarded as confounding factors for LRFS: R0 resection and (neo)adjuvant radiotherapy (Table 2). In addition, three parameters were associated with MRFS and were regarded as con-

TABLE 2 Impact of characteristics unbalanced according to re-excision categories on LRFS and MFRS

Categories	5-year LRFS	p value	5-year MRFS	p value
Female	75.3 ± 5.6	0.450	92.1 ± 3.2	0.429
Male	74.0 ± 6.0		89.7 ± 3.2	
Lower limb primaries	76.3 ± 8.7	0.312	89.3 ± 5.5	0.144
Truncal primaries	72.0 ± 7.9		92.9 ± 4.4	
Upper limb primaries	73.8 ± 6.9		91.0 ± 4.9	
No muscle involvement	73.3 ± 6.0	0.272	92.1 ± 2.7	0.515
Muscle involvement	77.7 ± 11.0		89.1 ± 3.3	
Tumor size ≤ 50 mm	75.1 ± 6.0	0.692	92.2 ± 3.0	0.014
Tumor size > 50 mm	74.0 ± 5.9		92.9 ± 3.4	
Superficial tumor	73.9 ± 6.1	0.517	93.0 ± 4.0	0.003
Deep tumor	64.0 ± 9.7		89.8 ± 3.3	
Liposarcoma	77.1 ± 9.8	0.127	93.2 ± 5.5	0.130
Leiomyosarcoma	75.8 ± 8.9		91.8 ± 5.4	
Myxofibrosarcoma	68.0 ± 8.2		92.1 ± 6.6	
Synovial sarcoma	84.0 ± 10.1		93.0 ± 6.7	
Other sarcomas	73.4 ± 8.7		89.1 ± 4.9	
Grade 1	86.4%	0.162	100%	0.006

TABLE 2 continued

Categories	5-year LRFS	*p* value	5-year MRFS	*p* value2
Grade 2	73.7%		94.3%	
Grade 3	72.1%		87.8%	
R1 resection	61.7 ± 5.6	0.0001	88.7 ± 4.0	0.067
R0 resection	83.8 ± 7.7		91.5 ± 3.2	
No radiotherapy	60.4 ± 6.0	0.0001	92.1 ± 3.6	0.032
(Neo)adjuvant radiotherapy	85.5 ± 9.0		90.7 ± 3.9	
No chemotherapy	74.2 ± 5.8	0.979	91.5 ± 3.3	0.190
(Neo)adjuvant chemotherapy	78.2 ± 12.1		88.9 ± 5.0	

LRFS local recurrence-free survival, *MRFS* metastatic relapse-free survival

founding factors for MRFS: tumor over 50 mm in size, deep tumor, and (neo)adjuvant radiotherapy.

Multivariate and Stratified Analyses

Multivariate analysis demonstrated that Group A patients showed significantly improved LRFS ($p = 0.0001$) (Table 3) after taking into account confounding factors such as R0 resection and (neo)adjuvant radiotherapy. Multivariate analysis also showed that RE in SRCs did not influence MFRS ($p = 0.367$) after taking into account confounding factors such as tumor size, deep tumor, and (neo)adjuvant radiotherapy. Figure 2 depicts the impact of adjuvant radiotherapy in Group A ($p = 0.098$), Group B ($p = 0.015$), and Group C patients ($p = 0.001$).

Management of the Local Relapse and Amputation Rate

During follow-up, 123 patients experienced a first LR: 28/300 in Group A, 15/71 in Group B, and 80/251 in Group C ($p = 0.00001$) (Fig. 1b). All these patients required further surgical procedures, and six required a limb amputation: 0/28 patients in Group A, 1/15 (6.6%) patients in Group B, and 5/80 (6.2%) patients in Group C ($p = 0.41$). A second relapse occurred in 23 patients during follow-up: 6/28 patients in Group A, 2/15 patients in Group B, and 15/80 patients in Group C ($p = 0.81$). Following this second relapse, amputation was ultimately necessary in two patients in each group (2/6, 2/2, and 2/15 for Groups A, B, and C, respectively; $p = 0.26$).

DISCUSSION

The key findings of our study were (1) a watch and wait approach to RE for selected patients after UE does not impair MRFS, OS, or amputation rate; (2) systematic RE after UE, if performed by an expert surgeon, significantly improves local control; and (3) radiotherapy improves LRFS, and the magnitude of its gain is inversely proportional to the quality of surgery.

(1) *The Impact of Systematic RE on OS and MRFS* When there is a macroscopic residual tumor, or in cases of piecemeal resection, there is no doubt that RE must be performed. Arguments in favor of immediate RE for UE after complete marginal resection are that microscopic residual cells could increase metastatic risk and impair survival. Two studies[29,30] justified systematic RE by showing a correlation between local and metastatic control; however, those studies included cases with partial resection or surgical biopsy of high-grade sarcoma. Conversely, more recent studies[10,20,23,26,27,31,32] confirmed, as we identified, that local control is not correlated with metastatic relapse and does not affect OS for systematic RE. After UE, metastatic risk is estimated to be between 10%[23] and 33%,[20] and RE delayed at the time of LR (Group C) did not impair MRFS or OS. Indeed, in the univariate analysis, four factors were observed to be associated with significantly lower MRFS (tumor depth, tumor size, grade, and adjuvant radiotherapy), but only two of these factors (grade 2/3 and deep tumor) were significant in multivariate analysis. These results suggested that OS is not influenced by local management of STS.

(2) *Impact of RE on Local Control and Risk of Amputation* The 5-year LRFS was better when systematic RE was performed, especially if performed in SRCs. This observation stressed the fact that patients affected by STS must be referred to specialized sarcoma centers. The worse outcomes in Group B, compared with Group A, suggested that these difficulties might have been underestimated by non-expert surgeons, since RE can represent a clinical challenge. This surgical procedure requires the removal of all surgical beds and needs to be planned, ideally on (1) the basis of initial imaging, which is not always available; (2) the initial surgical procedure technique; and (3) post-

TABLE 3 Adjusted analysis of the impact of re-excision in sarcoma referral centers on LRFS and MRFS

Parameter	HR	95% CI	*p* value
LRFS			
(Neo)adjuvant radiotherapy	0.21	0.14–0.32	0.0001
R0 resection after first procedure	0.24	0.12–0.40	0.0001
Group A vs. Group C	0.44	0.24–0.83	0.0100
Group B vs. Group C	0.85	0.47–1.53	0.593
MRFS			
Tumor size over 50 mm	1.43	0.63–3.22	0.376
Deep tumor	3.09	1.08–7.98	0.034
(Neo)adjuvant radiotherapy	0.96	0.39–2.36	0.924
Group A vs. Group C	0.80	0.22–2.85	0.467
Group B vs. Group C	0.62	0.17–2.37	0.484
Grade 1 vs. Grades 2 and 3	2.13	1.12–4.02	0.020

LRFS local recurrence-free survival, *MRFS* metastatic relapse-free survival, *HR* hazard ratio, *CI* confidence interval

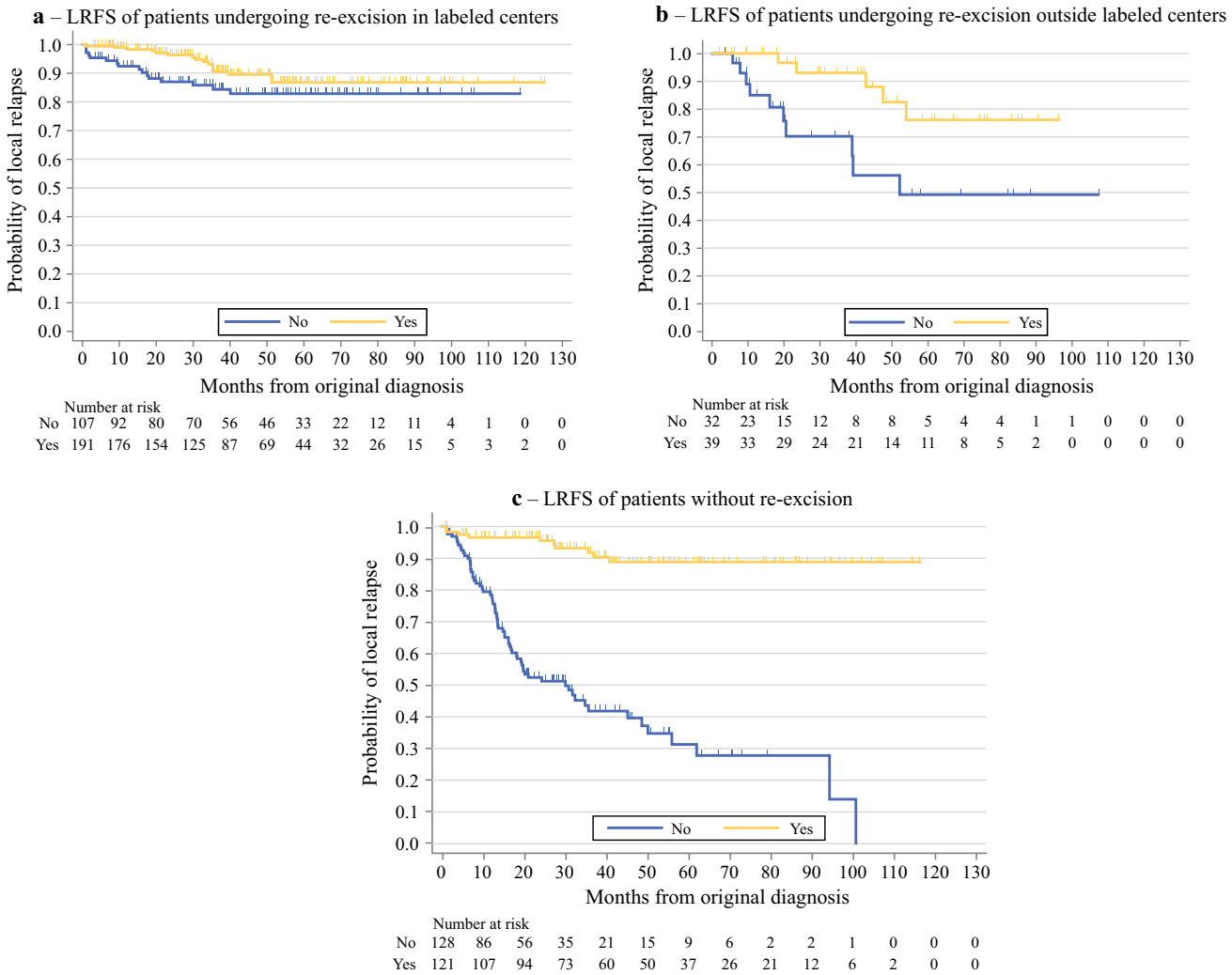

FIG. 2 Impact of radiotherapy on LRFS in patients **a** undergoing re-excision in labeled centers, **b** undergoing re-excision outside labeled centers, and **c** without re-excision. *LRFS* local relapse-free survival

surgical imaging, which describes the surgical and drainage paths that must be removed during the RE procedure. Several studies showed a high rate of R1 resections (up to 69%),[23,31,33] and higher morbidity[33] for systematic RE.

An advantage of delaying RE until the time of LR is that the surgery is better guided by the tumor mass compared with a 'blind' systematic RE. In this study, 63.8% of patients in Group C were spared from RE after 5 years of follow-up, without worsening of MRFS or OS, and these patients avoided an immediate useless surgery. Systematic RE can be a risky procedure, requiring a flap and reconstruction more frequently than for STS without UE (30% vs. 5% in the study by Potter et al.,[9] 42% vs. 22% in the study by Smolle et al.[10], and 71% vs. 41% in the study by Arai et al.[30]). Lastly, these procedures and their own morbidity are easier to justify to the patient once recurrence has occurred.

Although amputation has significant implications for patients (amputation occurred in 6% of the cohort), this was not found to be statistically significant. Moreover, this group of patients had inherently larger, higher grade and deeper cancers with poorer local prognostic factors, which could explain this rate. This bias in group C remains a limitation of this retrospective design.

(3) *Effects of Radiotherapy on LR (Fig. 2)* Radiotherapy independently improves LRFS. Its effect was particularly observed in Group C. This group mixed patients for whom a non-mutilating RE was not achievable (who received palliative adjuvant radiotherapy) and patients for whom a deliberate watch and wait approach was adopted, while RE would have been feasible. The difference was not feasible in this database. The analysis of LRFS for these patients without RE showed an acceptable local control, demonstrating the benefit compared with amputation. In others studies, the 5-year LRFS after this 'salvage radiotherapy' ranged from 66 to 88%.[31,34,35] Similarly, Group B patients also benefited from better local control by radiotherapy, but less significantly ($p = 0.015$). In Group A, although radiotherapy was more frequently used, LRFS did not differ between the subgroups with and without radiotherapy ($p = 0.098$). This suggests that radiotherapy improves LRFS; however, the magnitude of its gain is inversely proportional to the quality of surgery.

Study Limitations

The major limitations of the present study are inherent to its retrospective nature. Management within the sarcoma network is heterogeneous, reflecting the absence of consensus and shared guidelines for the management of patients after UE. Furthermore, management has evolved during the 10-year study period. Lastly, Group C matched two clinical situations, as indicated above. However, the database cannot depict all parameters that influenced the decision making retrospectively.

CONCLUSIONS

Systematic RE outside of community centers does not improve as well as LRFS in an SRC and should be avoided. A watch and wait strategy could be an option for selected patients after UE, if follow-up is feasible.

These results should be confirmed by further studies, with primary endpoints taking account of OS, MRFS, LRFS, amputation rate, and quality of life. Large multicentric propensity analysis could be performed and, ideally, a randomized study has to be initiated.

ACKNOWLEDGMENT The authors thank Loïc Lebellec, Francoise Ducimetiere, Antoine Giraud, and Séverine Marchant.

DISCLOSURE Gauthier Decanter, Eberhard Stoeckle, Charles Honore, Pierre Meeus, Jean Camille Mattei, Pascale Dubray-Longeras, Gwenael Ferron, Sébastien Carrere, Sylvain Causeret, Jean-Marc Guilloit, Magali Fau, Philippe Rosset, Jean-Christophe Machiavello, Jean Baptiste Delhorme, Nicolas Regenet, François Gouin, Jean-Yves Blay, Jean-Michel Coindre, Nicolas Penel, and Sylvie Bonvalot have no conflicts of interest to disclose.

REFERENCES

1. Pisters PW, Harrison LB, Leung DH, Woodruff JM, Casper ES, Brennan MF. Long-term results of a prospective randomized trial of adjuvant brachytherapy in soft tissue sarcoma. *J Clin Oncol*. 1996;14:859–68.
2. Yang JC, Chang AE, Baker AR, et al. Randomized prospective study of the benefit of adjuvant radiation therapy in the treatment of soft tissue sarcomas of the extremity. *J Clin Oncol*. 1998;16:197–203.
3. Casali PG, Abecassis N, Bauer S, et al. Soft tissue and visceral sarcomas: ESMO-EURACAN Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2018;29 Suppl 4:iv51–67.
4. Blay JY, Soibinet P, Penel N, et al. Improved survival using specialized multidisciplinary board in sarcoma patients. *Ann Oncol*. 2017;28:2852–9.
5. Italiano A, Le Cesne A, Mendiboure J, et al. Prognostic factors and impact of adjuvant treatments on local and metastatic relapse of soft-tissue sarcoma patients in the competing risks setting. *Cancer*. 2014;120:3361–9.
6. Italiano A, Delva F, Mathoulin-Pelissier S, et al. Effect of adjuvant chemotherapy on survival in FNCLCC grade 3 soft tissue sarcomas: a multivariate analysis of the French Sarcoma Group Database. *Ann Oncol*. 2010;21:2436–41.
7. Gronchi A, Ferrari S, Quagliuolo V, et al. Histotype-tailored neoadjuvant chemotherapy versus standard chemotherapy in patients with high-risk soft-tissue sarcomas (ISG-STS 1001): an international, open-label, randomised, controlled, phase 3, multicentre trial. *Lancet Oncol*. 2017;18:812–22.
8. George S, Wagner AJ. Low levels of evidence for neoadjuvant chemotherapy to treat soft-tissue sarcoma. *JAMA Oncol*. 2018;4:1169–70.

9. Potter BK, Adams SC, Pitcher JD Jr, Temple HT. Local recurrence of disease after unplanned excisions of high-grade soft tissue sarcomas. *Clin Orthop Relat Res*. 2008;466:3093–100.
10. Smolle MA, Tunn PU, Goldenitsch E, et al. The prognostic impact of unplanned excisions in a cohort of 728 soft tissue sarcoma patients: a multicentre study. *Ann Surg Oncol*. 2017;24:1596–605.
11. Stoeckle E, Gardet H, Coindre JM, et al. Prospective evaluation of quality of surgery in soft tissue sarcoma. *Eur J Surg Oncol*. 2006; 32:1242–8.
12. Bonvalot S, Levy A, Terrier P, Tzanis D, Bellefqih S, Le Cesne A, et al. Primary extremity soft tissue sarcomas: does local control impact survival? *Ann Surg Oncol*. 2017;24:194–201.
13. Callegaro D, Miceli R, Bonvalot S, et al. Impact of perioperative chemotherapy and radiotherapy in patients with primary extremity soft tissue sarcoma: retrospective analysis across major histological subtypes and major reference centres. *Eur J Cancer*. 2018;105:19–27.
14. Gundle KR, Kafchinski L, Gupta S, et al. Analysis of Margin Classification Systems for Assessing the Risk of Local Recurrence After Soft Tissue Sarcoma Resection. *J Clin Oncol*. 2018;36:704–9.
15. McKee MD, Liu DF, Brooks JJ, Gibbs JF, Driscoll DL, Kraybill WG. The prognostic significance of margin width for extremity and trunk sarcoma. *J Surg Oncol*. 2004;85:68–76.
16. Ray-Coquard I, Thiesse P, Ranchère-Vince D, et al. Conformity to clinical practice guidelines, multidisciplinary management and outcome of treatment for soft tissue sarcomas. *Ann Oncol*. 2004;15:307–15.
17. Tedesco NS, Henshaw RM. Unplanned resection of sarcoma. *J Am Acad Orthop Surg*. 2016;24:150–9.
18. Alamanda VK, Delisca GO, Archer KR, Song Y, Schwartz HS, Holt GE. Incomplete excisions of extremity sts are unaffected by insurance status or distance from a sarcoma center. *J Surg Oncol*. 2013;108:477–80.
19. Davis AM, Kandel RA, Wunder JS, et al. The impact of residual disease on local recurrence in patients treated by initial unplanned resection for soft tissue sarcoma of the extremity. *J Surg Oncol.* 1997;66;81–7.
20. Rehders A, Stoecklein NH, Poremba C, Alexander A, Knoefel WT, Peiper M. Reexcision of soft tissue sarcoma: sufficient local control but increased rate of metastasis. *World J Surg*. 2009;33:2599–605.
21. Stojadinovic A, Leung DH, Hoos A, Jaques DP, Lewis JJ, Brennan MF. Analysis of the prognostic significance of microscopic margins in 2,084 localized primary adult soft tissue sarcomas. *Ann Surg*. 2002;235:424–34.
22. Trovik CS, Bauer HC, Alvegård TA, et al. Surgical margins, local recurrence and metastasis in soft tissue sarcomas: 559 surgically-treated patients from the Scandinavian Sarcoma Group Register. *Eur J Cancer*. 2000;36:710–6.
23. Koulaxouzidis G, Schwarzkopf E, Bannasch H, Stark GB. Is revisional surgery mandatory when an unexpected sarcoma diagnosis is made following primary surgery? *World J Surg Oncol*. 2015;13:306–16.
24. Pretell-Mazzini J, Barton MD Jr, Conway SA, Temple HT. Unplanned excision of soft-tissue sarcomas: current concepts for management and prognosis. *J Bone Joint Surg Am*. 2015;97:597–603.
25. von Mehren M, Randall RL, Benjamin RS, et al. Soft tissue sarcoma, version 2.2018, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw*. 2018;16:536–63.
26. Funovics PT, Vaselic S, Panotopoulos J, Kotz RI, Dominkus M. The impact of re-excision of inadequately resected soft tissue sarcomas on surgical therapy, results, and prognosis: a single institution experience with 682 patients. *J Surg Oncol.* 2010;102:626–33.
27. Bianchi G, Sambri A, Cammelli S, et al. Impact of residual disease after "unplanned excision" of primary localized adult soft tissue sarcoma of the extremities: evaluation of 452 cases at a single Institution. *Musculoskelet Surg*. 2017;101:243–8.
28. Bellera CA, Penel N, Ouali M, et al. Definition for the Assessment of Time-to-event Endpoints in Cancer Trials Initiative. Guidelines for time-to-event end point definitions in sarcomas and gastrointestinal stromal tumors (GIST) trials: results of the DATECAN initiative (Definition for the Assessment of Time-to-event Endpoints in CANcer trials). *Ann Oncol*. 2015;26:865–72.
29. Giuliano AE, Eilber FR. The rationale for planned reoperation after unplanned total excision of soft-tissue sarcomas. *J Clin Oncol*. 1985;3:1344–8.
30. Arai E, Nishida Y, Tsukushi S, Wasa J, Ishiguro N. Clinical and treatment outcomes of planned and unplanned excisions of soft tissue sarcomas. *Clin Orthop Relat Res*. 2010;468:3028–34.
31. Chandrasekar CR, Wafa H, Grimer RJ, Carter SR, Tillman RM, Abudu A. The effect of an unplanned excision of a soft-tissue sarcoma on prognosis. *J Bone Joint Surg B*. 2008;90:203–8.
32. Ueda T, Yoshikawa H, Mori S, Araki N, Myoui A, Kuratsu S, et al. Influence of local recurrence on the prognosis of soft-tissue sarcomas. *J Bone Joint Surg Br*. 1997;79:553–7.
33. Noria S, Davis A, Kandel R, Levesque J, O'Sullivan B, Wunder J, et al. Residual disease following unplanned excision of soft tissue sarcoma. *J Bone Joint Surg Am*. 1996;78:650–5.
34. Kepka L, Suit HD, Goldberg SI, Rosenberg AE, Gebhardt MC, Hornicek FJ, et al. Results of radiation therapy performed after unplanned surgery (without re-excision) for soft tissue sarcomas. *J Surg Oncol*. 2005;92:39–45.
35. Zagars GK, Ballo MT, Pisters PW, Pollock RE, Patel SR, Benjamin RS. Surgical margins and reresection in the management of patients with soft tissue sarcoma using conservative surgery and radiation therapy. *Cancer.* 2003;97:2544–53.