



## Soft tissue sarcoma in children, adolescents and young adults: Outcomes according to compliance with international initial care guidelines

C. Collignon, M. Carton, H.J. Brisse, S. Pannier, A. Gauthier, S. Sarnacki, B. Tiléa, A. Savignoni, S. Helfre, P. Philippe-Chomette, et al.

### ► To cite this version:

C. Collignon, M. Carton, H.J. Brisse, S. Pannier, A. Gauthier, et al.. Soft tissue sarcoma in children, adolescents and young adults: Outcomes according to compliance with international initial care guidelines. EJSO - European Journal of Surgical Oncology, 2020, 46, pp.1277 - 1286. 10.1016/j.ejso.2019.11.518 . hal-03490731

HAL Id: hal-03490731

<https://hal.science/hal-03490731>

Submitted on 22 Aug 2022

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial 4.0 International License

1           **SOFT TISSUE SARCOMA IN CHILDREN, ADOLESCENTS AND YOUNG**  
2           **ADULTS: OUTCOMES ACCORDING TO COMPLIANCE WITH**  
3           **INTERNATIONAL INITIAL CARE GUIDELINES**

4  
5       **Authors:** C. Collignon<sup>1</sup>, M. Carton<sup>2</sup>, H.J. Brisse<sup>3</sup>, S. Pannier<sup>4</sup>, A. Gauthier<sup>5</sup>, S. Sarnacki<sup>6</sup>, B.  
6       Tiléa<sup>7</sup>, A. Savignoni<sup>2</sup>, S. Helfre<sup>8</sup>, P. Philippe-Chomette<sup>9</sup>, L. Cardoen<sup>3</sup>, O Boccara<sup>10</sup>, G.  
7       Pierron<sup>11</sup>, D. Orbach<sup>1</sup>

8  
9       **Affiliations:** 1. SIREDO Oncology Center (Care, Innovation and Research for Children,  
10      Adolescents and Young Adults with Cancer) Institut Curie, PSL University, Paris, France. 2.  
11      Department of Biostatistics, Institut Curie, PSL University, Paris, France. 3. Imaging  
12      Department, Institut Curie, Paris, France. 4. Department of Orthopedic Pediatric Surgery,  
13      Necker Enfants Malades Hospital, Paris, France. Paris Descartes University, Sorbonne Paris  
14      Cité, Paris, France. 5. Department of Pathology, Institut Curie, Paris, France. 6. Department  
15      of Pediatric Surgery and Urology, Necker Enfants Malades Hospital, Paris, France. Paris  
16      Descartes University, Sorbonne Paris Cité, Paris, France. 7. Department of Radiology, Robert  
17      Debré Hospital, Paris, France. 8. Department of Radiotherapy, Institut Curie, Paris, France. 9.  
18      Department of Pediatric Surgery, Robert Debré Hospital, Paris, France. 10. Department of  
19      Dermatology and Reference Center for Genodermatoses and Rare Skin Diseases (MAGEC),  
20      Université Paris Descartes, Sorbonne Paris Cité, Institut Imagine, Hôpital Universitaire  
21      Necker-Enfants Malades, 11. Department of Somatic Genetics, Institut Curie, Paris, France.

22  
23       **Correspondence:** Charlotte Collignon, Pediatric, Adolescent, and Young Adult Oncology  
24      Department, Institut Curie, 26, rue d'Ulm, 75005 Paris, France. E-mail:  
25      charlotte.collignon@aphp.fr

26       **Key words:** Soft tissue Sarcoma; Pediatric cancer; Diagnostic Pathway; initial care

27       **Running title:** Diagnostic guideline compliance for pediatric soft tissue sarcomas

28   **ABSTRACT**  
29

30   **Background:** Outcomes for adults with soft tissue sarcoma are better when managed at  
31   referral centers. Care guidelines advise for 5 main criteria: 1-Imaging before biopsy; 2-Tumor  
32   biopsy before surgery; 3-Multidisciplinary team discussion (MTD) before biopsy; 4-Biopsy in  
33   “expert centers”; 5-Somatic molecular biology feasible. The aim is to describe and assess the  
34   prognostic impact of initial management of STS according to the type of referring centers and  
35   the number of optimal criteria.

36   **Methods:** Monocentric retrospective analysis of the management of 127 youths (0-25 years)  
37   with localized STS treated from 2006 to 2015.

38   **Results:** Median age at diagnosis was 9.6 years (range: 0-25). Overall, only 39% patients had  
39   5/5, 3-4: 29%,  $\leq 2$ : 32%. No imaging was performed before surgery/biopsy for 21% patients,  
40   no biopsy before surgery for 35%. Patients referred by “expert centers” had higher  
41   compliance to guidelines ( $P=0.025$ ). Upfront surgery was performed in 59/127 patients.  
42   Immediate re-operation was inversely related to the number of criteria (0% when 5 criteria vs.  
43   14% for 3-4, 46% if  $\leq 2$ ;  $P<0.001$ ). For malignant tumors, outcome was better when 5 criteria  
44   were reached: 5 year EFS 90.8% (81.4-100.0%) vs. 71.6 for (60.4-84.9%;  $\leq 4$  criteria;  $p=$   
45   0.033), OS 93.6% (85.5-100%) vs. 79.5% (68.9-91.8%;  $p= 0.11$ ), and LRFFS 90.6% (81.0-  
46   100.0) vs. 73.1% (62.0-86.3%;  $p= 0.047$ ).

47   **Conclusion:** Less than half of the youths with STS are initially managed according to  
48   international guidelines, highlighting the need for better information about optimal  
49   management. These results plead for immediate management in reference centers to reduce  
50   initial burden of therapy.

51   **Acknowledgments:** M. Wisnia for his financial support.

52

53

54

55

56 **INTRODUCTION**

57       The most frequent soft tissue masses occurring during childhood are benign and could  
58   be observed or treated with conservative surgery. This group chiefly includes vascular tumors  
59   or malformations, fibrous and fibrohistiocytic tumors and pseudotumors (1). Soft Tissue  
60   Sarcomas (STS) are a rare and heterogeneous group of childhood cancers in terms of clinical  
61   presentation, histology and molecular biology. Their prevalence is estimated around 9.6 to 11  
62   patients per million per year in children and 13.7 in adolescents (2)(3). This group of STS  
63   represents around 6 to 7% of all cancers under 20 years of age (2)(3). The 2013 World  
64   Health Organization defined sarcomas in three main groups: malignant tumors, intermediate  
65   rarely metastasizing and intermediate locally aggressive soft tissue tumors; (4). Sometimes,  
66   benign and malignant lesions can present with a similar clinical picture, but due to being rare,  
67   malignant lesions are often misdiagnosed. This leads to significant delays in treatment. . A  
68   study of young patients referred to an oncologic pediatric center for a superficial and palpable  
69   soft tissue mass, estimated 44% of malignant tumors, 32% of benign tumors and 24% of  
70   pseudotumoral lesions (5). Among soft tissue malignancies and intermediate tumors,  
71   immediate first-line strategy could be very different according to the histological subtype:  
72   initial neoadjuvant chemotherapy, immediate surgery or observation. Thereby, in children  
73   with superficial palpable soft tissue lumps, most of the time, a definitive diagnostic requires a  
74   biopsy, since both clinical and radiological findings are frequently nonspecific (1). However,  
75   this biopsy should be performed after ruling out typical patterns of benign soft tissue lesions,  
76   excluding pseudotumors and some so-called “don’t-touch-me” lesions (1). To optimize initial  
77   diagnostic care, consensual guidelines have been developed for adults with suspected  
78   sarcomas and define optimal criteria for a patient with a soft tissue mass (6). Various studies  
79   identified the favorable impact of initial specialized networks in the diagnosis pathway for  
80   adults with sarcomas (7)(8)(9). These specialized centers or reference networks are defined by

81 their multidisciplinary expertise and the high number of patients treated for sarcomas. These  
82 recent studies revealed that adult patients addressed to specialized centers prior to any local  
83 intervention had a significantly higher rate of better management according to international  
84 recommendations, which strongly influenced their outcome (8)(9). A strong correlation was  
85 therefore seen between early multidisciplinary tumor board discussions and favorable  
86 prognosis (7)(10). Until now, no specific diagnostic pathway has been set-up or analyzed in  
87 children or adolescents.

88 The objective of this study is to describe the quality of the diagnostic pathways in young  
89 patients treated for a localized superficial soft tissue sarcoma according to the initial site of  
90 care, as well as analyze its influence on local treatment intensity and outcome.

91

## 92 MATERIAL AND METHODS

### 93 *Study Population*

94 We retrospectively retrieved information from the medical charts of consecutive  
95 patients under the age of 25 years old treated at the Institut Curie, Paris (SIREDO Oncology  
96 Center) between 2006 and 2015, diagnosed with a localized (namely, with possible lymph  
97 node involvement, but without distant metastases), soft tissue sarcoma or intermediate grade  
98 tumors located in the limbs, trunk wall or scrotum, or a palpable sarcoma in the head and  
99 neck. The anatomic location was defined on clinical presentation with a distinction regarding  
100 “superficial” (i.e. palpable regardless of its anatomical depth, subcutaneous, subaponeurotic)  
101 versus “deep” (i.e. non-palpable or internal lesions). Deep intra- or retroperitoneal abdominal  
102 sarcomas, intra-thoracic sarcomas and deep-seated tumors in the head and neck were not  
103 included. We focused on pediatric patients with superficial palpable lesions because patients  
104 with deep-seated intra-abdominal, intra-thoracic or head and neck lesions are often rapidly  
105 directly referred to specialized centers after the initial imaging. Hence, for such locations the

106 risk of initial malpractice remains exceptional, whereas inappropriate upfront surgery is  
107 frequently performed for superficial tumors. We included only non-metastatic lesions in order  
108 to better estimate the impact of the initial optimal care, because prognostic for metastatic  
109 sarcomas are more related to the distant lesions' evolution than local primary control (11).

110 Sarcomas were defined on histological examination after a biopsy or surgical resection  
111 and included all highly malignant or intermediate locally aggressive (desmoid-type  
112 fibromatosis, dermatofibrosarcomas, myofibroblastic inflammatory tumors,  
113 congenital/infantile fibrosarcomas, Kaposi sarcomas, atypical fibroxanthomas, low-grade  
114 fibromyxoid sarcomas) soft tissue tumors according to WHO classification 2013 (12).  
115 Patients only referred to the Institut Curie after a relapse for radiotherapy, a second opinion or  
116 for a trial inclusion were not included. The SIREDO Oncology Center is one of 3 centers  
117 practicing Pediatric Oncology in Ile-de-France (12.2 million inhabitants in 2019, including  
118 3.13 million under 20 years old). It takes care of patients from 0 to 25 years with all solid  
119 tumors, including lymphoma, but not leukemia. A specific diagnostic pathway (i.e.,  
120 "CUSTOM" for *Curie Sarcomes et Tumeurs complexes des Os et des tissus Mous*) dedicated  
121 to all patients with soft tissue masses was created in 2007 in our institution (5). Any patient of  
122 any age with an undetermined soft tissue or bone lesion can be referred to the CUSTOM  
123 consultation and, in less than 10 days, have specialized pediatric radiologists review the  
124 examinations that were already carried out, any potential additional examinations when  
125 necessary (standard X-ray, soft tissue ultrasound, or MRI) and, if applicable, cytological or  
126 histological analyses via image-guided fine needle aspiration (FNA) or core needle biopsy  
127 (CNB) under local or general anesthesia.

128

129

130      *Data selection*

131            The patients list was extracted from the Institut Curie's PMSI (*Programme de*  
132        *Médicalisation du Système Informatique*). This study complied with reference methodology  
133        MR-004 from the *Commission Nationale de l'Informatique et des libertés (CNIL)*. Approval  
134        from an institutional review board was obtained for the study. Patient records and information  
135        were made anonymous.

136      *Clinical Practice Guidelines (CPG)*

137            Five guidelines were selected from the ESMO recommendations for soft tissue  
138        sarcoma in adults to define optimal diagnosis and initial treatment (6): 1-Adequate imaging  
139        (MRI, CT scan and/or US) performed before any biopsy or surgery (1); 2- Biopsy performed  
140        before any surgery, except for paratesticular locations for which immediate surgery is  
141        advised; 3- A multidisciplinary team discussion (MTD) carried out before any biopsy/surgery;  
142        4- Biopsy/surgery performed by a specialist physician working in an “expert center” including  
143        the Institut Curie or any University Hospitals (CHU) regularly participating in the regional  
144        pediatric MTD (called *CANPEDIF-RCPPI; Cancer pédiatrique d'Ile de France - reunion de*  
145        *concertation pluridisciplinaire d'Ile de France*); 5- Adequate tumor samples available  
146        allowing for molecular biology analyses.

147      *Data collection*

148            All patient characteristics, diagnostic pathways, treatments and outcomes were  
149        extracted from medical charts. Patients were classified according to the international  
150        classification of specific tumor sites (13). Clinical staging was defined according to the  
151        Tumor Node Metastases (TNM) system (14): T1 or T2 according to the invasion of  
152        contiguous organs; N0/N1, and M0/M1 according to the presence of lymph nodes or distant  
153        metastases. Tumor size was defined clinically and with imaging. Lymph node involvement

154 was assessed clinically and confirmed with cyto-aspiration or nodal dissection when needed.  
155 M1-patients were not included in the analysis.

156 All patients were treated according to their histological subtype in compliance with  
157 international guidelines or ongoing protocols (15)(16)(17)(18). The surgical resection system  
158 from the *Union Internationale Contre le Cancer* (UICC) was used to define the quality of  
159 surgery: R0 =macroscopically complete resection; R1 =tumor cells visible on resection  
160 margins; R2 =macroscopic residual disease (19). A mutilating surgery was defined either as a  
161 major resection such as an exenteration or an amputation with functional impairment.

162 *Statistical Analysis*

163 All data were analyzed using descriptive statistical methods and the proportion of  
164 patients within each group of characteristics was compared using the chi-squared or Fisher's  
165 exact test, when appropriate. A p-value less than 0.05 was considered statistically significant.  
166 Survival time was calculated from the date of diagnosis to the time of the last follow-up or  
167 event. Local or lymph node tumor progression or relapse, and death by any cause were  
168 considered as Loco-Regional Relapse-Free Survival (LRRFS). Overall survival (OS) was  
169 measured from the date of diagnosis to death for any reason. Event-Free Survival (EFS) was  
170 measured from the date of diagnosis to the time of the last follow-up or event: local or lymph  
171 node or metastatic tumor progression and death by any cause. All of them were estimated  
172 using the Kaplan–Meier method and median follow-up duration using the reverse Kaplan–  
173 Meier method. Survival curves with their log-rank tests were generated.

174 **RESULTS**

175 *Patients and diagnostic pathway characteristics*

176 Among the 277 patients treated in our center for a sarcoma during this period, 127  
177 patients fulfilled inclusion criteria (Figure 1). Patients and tumor characteristics with the  
178 provided therapies are detailed in Table I. Overall, 68.5% were malignant sarcomas and  
179 31.5% intermediate locally aggressive tumors. Median age was 9.6 years (range, 0-25).  
180 Overall, 82% were less than 15 years old. Sex ratio was 1.6 in favor of males.

181 Twenty patients (16%) had a medical history: one Gorlin's syndrome associated to  
182 rhabdomyosarcoma (RMS), one Gardner's syndrome with a desmoid-type fibromatosis, and  
183 one type-1 neurofibromatosis associated with a Malignant Peripheral Nerve Sheath Tumor  
184 (MPNST). In addition, 3 patients had personal history of unrelated associated developmental  
185 disorders. Primary sites were mainly limb (50%), head and neck (28%) and thorax (9%). Most  
186 tumors were ≤ 5 cm (60%) without clinical lymph node involvement (77%). According to  
187 WHO classification, 69% of patients had malignant sarcomas and 31% intermediate tumors.  
188 The most common histological subtypes were RMS (29%), desmoid-type-fibromatosis (21%)  
189 and synovial sarcoma (11%) (Figure 2).

190 The primary medical contact was mostly the general practitioner (60%), emergency  
191 units (25%) or surgical centers (9%). Median delays were 2.7 months (range, 0-81.7) between  
192 initial clinical symptoms and first medical contact, 0.2 months (range, 0-26.5) between first  
193 medical care and MTD, and 2.8 months (range, 0-121.3) between initial symptoms and final  
194 diagnosis. Seventy-seven patients (61%) then received their first diagnostic care in an “expert  
195 center” (RCPPI centers 36 cases or Institut Curie 41 cases;), whereas 50 patients (39%) were  
196 first managed in a general surgical hospital or other centers such as clinics. The compliance  
197 with each criterion according to the place of initial care is detailed in Table II.

198

199

200    *Compliance with Clinical Practice Guidelines (CPGs)*

- 201    - Criterion 1 (MRI or CT scan before biopsy or surgery): most patients (105 cases; 83%)  
202       had a CT scan or MRI before biopsy or surgery but 22 patients only received an  
203       ultrasound or no imaging (18%).
- 204    - Criterion 2 (biopsy before any treatment): upfront biopsy performed for 88 patients  
205       (69%), while 37 patients had no biopsy (29%). Fine needle core biopsies were performed  
206       for 42 patients, surgical biopsies for 34 patients, a punch superficial biopsy for one patient  
207       and not specified for 11 patients.
- 208    - Criterion 3 (biopsy or surgery after MTD): Overall 77 patients (61%) received a MTD  
209       before any biopsy or surgery. Among the 88 patients who had an initial biopsy, only 29  
210       cases (34%) were previously discussed in an MTD.
- 211    - Criterion 4 (biopsy performed in specialized center): Biopsies were performed in “expert  
212       centers” for only 64 patients (50%), i.e., for 41 cases (32%) at the Institut Curie, and 23  
213       cases (18%) in surgical expert centers.
- 214    - Criterion 5 (molecular biology): molecular biology analyses were available for 99 patients  
215       (78%).

216       Overall, CPGs during the initial diagnostic pathway were in total compliance for only  
217       52 patients (5 criteria, 41%), 36 patients respected 3 or 4 criteria (28%) and 39 had 2 or less  
218       (31%) (Figure 3). There was a significant difference according to patient’s age (Figure 4).  
219       Compliance with CPGs was significantly better when initial diagnostic management was  
220       performed in expert centers ( $p < 0.01$ ; Figure 5).

221    *Treatment*

222       Overall, 100 patients (79%) had surgery for the primary, i.e., 59 at diagnosis and 41  
223       after neoadjuvant therapy. Among the 87 patients with a malignant sarcoma, 80 (92%) were

224 treated with surgery, 65 had chemotherapy (75%) and 50 received radiotherapy (59%).  
225 Among the 40 patients treated for an intermediate malignancy, 20 (50%) had surgery, 13 had  
226 chemotherapy (33%) and 2 received radiotherapy (5%).

227 Among the 59 patients (46%) treated with immediate primary surgery, only 16 (27%)  
228 had a prior histological diagnosis obtained after an initial biopsy. Overall, 16 had R0 margins  
229 (27%), 30 R1 margins (51%), 10 R2 margins (17%) and 3 were missing data. Twenty-four  
230 patients out of 59 (41%) underwent immediate reoperation after diagnosis (R0 margins 20  
231 cases; R1 margins 2 cases; R2 margins and undetermined, 1 case each). Delayed surgery after  
232 first-line chemotherapy was performed for 10 of these patients. The surgical strategy was  
233 modified due to the inadequate initial pathway for 29 patients (23%): new surgeries (29 cases)  
234 and wider excision (11 cases). There was a significant relationship between the need for  
235 reoperations and the number of initially fulfilled optimal criteria with the following dose-  
236 response relationship: 6.0 % when 5 CPGs criteria were present, 25.0 % for 3-4 criteria and  
237 56.4% for  $\leq 2$  ( $P < 0.001$ ; Table III). The compliance rate with CPGs was not significantly  
238 associated with the need for radiotherapy: 50% for 5/5 criteria vs. 30.6% for 3-4 criteria and  
239 41% for  $\leq 2$ ; ( $P=0.2$ ).

240 *Overall survival and Loco-Regional Relapse-Free survival*

241 After a median follow-up of 71.5 months, (95% CI: 64.3-81.5), 109 patients (86%)  
242 reached complete remission (CR) or “no evidence of disease.” Tumor relapses were reported  
243 in 28 patients: 17 local, 10 regional lymph nodes, 1 combined, 3 isolated metastases and 7  
244 loco-regional with metastasis. Death occurred in 14 patients. Among the 113 patients living at  
245 the end of the follow-up, 91 remained in persistent first CR, 4 are in subsequent CR (no more  
246 tumor after second-line therapy following a relapse)), 3 had a stable residue and 15 had a  
247 progressive disease. OS at 5 years is 88.4% (95% CI: 82.6-94.6%). LRRFS at 5 years is

248 79.6% (95% CI: 72.8-87.1%). There was no statistical significant difference in terms of OS  
249 according to the number of CPG criteria fulfilled (93.1% for 5 criteria vs. 84% for 3-4 and  
250 86.1% if  $\leq 2$ , P= 0.265) or for LRRFS (82% when 5 criteria vs. 76.7% when 3-4 and 79.2%  
251 when  $\leq 2$ , P= 0.75) when all tumors were considered. After stratification on tumor size, there  
252 was a significant difference on OS and EFS according to the number of CPG criteria fulfilled  
253 for small tumors (Figure 6-7, Table IV-VI)-. For malignant tumors, there was statistical  
254 significant differences on EFS and LRRFS according to the number of CPG criteria fulfilled  
255 (Tables IV-VI; Figures 8-9). In addition, OS, EFS and LRRFS were not statistically different  
256 according to the number of CPG criteria when only intermediate tumors or when patients' age  
257 ( $\pm 10$  year) were considered (Tables IV-VI).

258 **DISCUSSION**

259 In this study, we report that only 41% of young patients with STS are correctly  
260 managed according to international guidelines, which has a significant impact on the burden  
261 of therapy through the increased rate of immediate primary reoperations. In addition, the  
262 outcome of patients with small tumors and malignant sarcomas are strongly influenced by the  
263 quality of the diagnosis pattern. It is possible that small tumors are difficult to be clinically  
264 considered initially as a potential cancer by the physician and this unspecific clinical  
265 presentation may lead to inadequate care at diagnosis. The reasons why compliance is not  
266 optimal is not precisely known, but is probably explained by the rarity of STS in children  
267 compared to benign lesions, as well as the lack of knowledge regarding the optimal ESMO  
268 guidelines in non-specialized physicians. Indeed, STS are rare tumors, especially in children,  
269 and frequently are present as isolated masses (1)(3). They often have no associated signs of  
270 malignancy such as a hard consistency, fast evolution, lymph nodes and general signs (5).  
271 Due to their rarity, they are often misrecognized and the diagnosis delay is long. Although

optimal CPGs are frequently reported in the literature over the years, the diagnostic pathway for patients with STS often does not follow these recommendations, even in adults (20). Adequate CPGs recommend multidisciplinary management for any soft tissue tumor as soon as the clinical and radiological presentation is not consistent with a typical benign lesion (6). However, patients are initially frequently managed outside reference centers (20). Notably, in our experience, 39% of pediatric patients were initially not managed in specialized centers. In France, *NetSarc* was created in 2009 to improve and homogenize the management of French patients with sarcomas, by building a large clinical national adult network including 28 reference centers sharing a common database (21). It gathers clinical and pathological data from patients treated for soft tissue and visceral sarcomas, which is then discussed in sarcoma multidisciplinary committees. After 10 years, it was demonstrated that patients initially managed in expert *Netsarc* centers had a higher rate of compliance with CPGs, a better LRRFS as well as higher rates of complete R0 surgery and less need for reoperations (5.5% when a *NetSarc* MTD was held before surgery vs. 15.3% after, in a series of 12,528 patients; p<0.0001)(7)(9). The quality of initial resection is a recognized strong prognostic factor in soft-tissue sarcomas: R2 and R1 margins are associated with more relapses despite any further oncological management (22). Unplanned excisions (so-called “whoops” procedures) are associated with more local relapses despite further treatments (23). International Guidelines therefore recommend referring every patient with a soft tissue tumor (deep-seated tumors or superficial masses larger than 3 to 5 cm) to a specialized center before any treatment. However, the diagnostic course and its impact on survival in children are still unknown. In our experience, about one-third of patients get unplanned surgery without prior histological diagnosis, whereas a precise biopathological diagnosis is mandatory to define the most appropriate treatment (24)(25). Molecular biology is especially mandatory nowadays in order to confirm many diagnoses, especially in cases of undifferentiated sarcomas, and might be

297 jeopardized by the inadequate management of the surgical/biopsy tumor specimen (i.e.,  
298 without frozen tissue) in a non-specialized center(26). Therefore, a multidisciplinary team in  
299 an expert center should ideally manage a child referred for a soft tissue lump before any  
300 surgery or biopsy.

301 To have a more homogenous population, and analyze the impact of a non-optimal  
302 diagnosis pathway on patients with potential soft part tumors, we focused our population on  
303 localized superficial palpable masses that could frequently be difficult to diagnose. Moreover,  
304 in children, abdominal tumors are rarely sarcomas and this location mainly concerns  
305 neuroblastoma or nephroblastoma. In addition, retroperitoneal or abdominal solid masses are  
306 less frequently operated on immediately without diagnosis and most of these young patients  
307 with such primary are automatically referred to expert centers before any biopsy. This,  
308 however, may be a limitation in our study, with a selection bias. In addition, our monocentric  
309 study with retrospective analysis only concerns a total of 127 patients. Therefore, our results  
310 need to be confirmed in a larger population.

311 Clinical examinations, conventional radiography and Doppler ultrasounds represent  
312 first-line examinations and are sometimes enough to provide a precise diagnosis for  
313 pseudotumors, vascular benign tumors or vascular malformations. In all other situations, an  
314 MRI is mandatory in order to establish the anatomic location of the mass, its potential  
315 aggressiveness and its local extension. A CT scan is much less accurate for soft tissue analysis  
316 and should not be the primary method, except in rare indications such as myositis ossificans.  
317 The radiologist's expertise plays a key role because many benign diagnoses can be provided  
318 according radiological arguments without a biopsy (1)(5). When a biopsy is needed, initial  
319 imaging is mandatory to define the best biopsy tract and select the optimal target area,  
320 avoiding necrotic zones. The lack of adequate imaging before upfront surgery is associated  
321 with potential serious adverse consequences. It might lead to more local treatments and

322 prevents a precise evaluation of the size and depth of the tumor, which might result in a  
323 mutilating reoperation or a broader surgery than initially needed (27). Furthermore, when an  
324 immediate, limited and unplanned surgery is carried out, it is more likely to have  
325 contaminated margins, which might indicate the need for complementary radiotherapy in case  
326 of sarcomas (27)(28). In these cases, the radiotherapy fields are difficult to define precisely  
327 and, most of the time, need to be enlarged. Moreover, the analysis of the initial tumor size and  
328 the response to chemotherapy, which are strong prognostic factors in most pediatric sarcomas,  
329 could not be correctly assessed. In this study, we have seen that most pediatric patients (83%)  
330 have adequate imaging before local biopsy or surgery.

331 We showed that patients with initial care in “expert centers” have a higher compliance  
332 with optimal CPGs, which corresponds to improved survival in large adult studies (7). In our  
333 study we have been able to demonstrate a direct benefit on OS or LRRFS, for small tumors  
334 and for malignant sarcomas probably because small tumors are more likely to be considered  
335 as benign lesions and, therefore, are more likely to be immediately operated on. The relatively  
336 limited number of patients or the few events reported, associated with the over-representation  
337 of non-aggressive tumors such as desmoid-type tumors, may explain why this value  
338 disappeared when the general population is considered. We, however, demonstrated that a  
339 higher compliance with CPGs is associated with less need for local reoperations, which  
340 reduces the total burden of therapy in children and better outcomes. In our study, about 23%  
341 of patients had their surgical treatment modified with an initial diagnosis pathway. These  
342 results demonstrate that every pediatric patient with an unexplained soft tissue lesion receive  
343 early referrals to expert centers. Furthermore, incomplete resections of certain tumors such as  
344 desmoid-type fibromatosis might result in residual genetically altered cells able to activate  
345 soft tissue repair mechanisms after trauma. Surgery might act like a trauma and be responsible

346 for tumor growth. In such tumors, a “wait-and-see” strategy after a biopsy is now  
347 recommended (29).

348 Overall prognosis of STS, including metastatic diseases, is estimated at around 70.6%  
349 survival after five years (30). To date, it depends on many tumor risk factors, most of them  
350 better identified in adults studies: high tumor grade, size > 5 cm, site of occurrence, tumor  
351 spread, age > 10 years at diagnosis, surgical margin > R0 (31). In addition, recent experiences  
352 showed that the quality of initial care strongly influenced outcome in adults and could be  
353 added to this list of unfavorable prognostic factors (7)(9)(21). In our study, patients over 15  
354 years old had less adequate diagnosis pathways than children, which is often reported in the  
355 literature (32). In some pediatric studies, diagnosis delays were estimated to have the potential  
356 to be reduced for around half of patients through better organization and with possible  
357 consequences on patient’s survival (33)(34)(35).

358  
359 **CONCLUSIONS**  
360

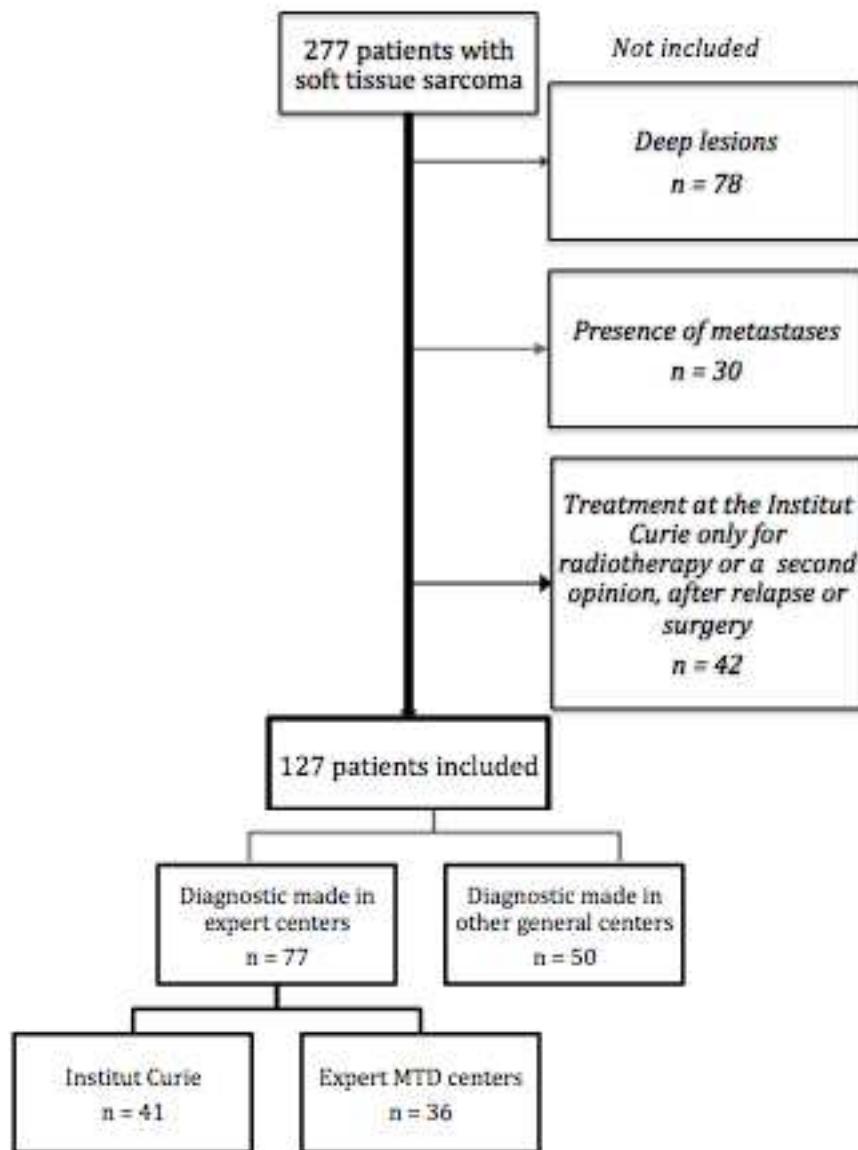
361 To improve compliance, we need to first improve the knowledge of pediatricians,  
362 general practitioners, surgeons, dermatologists and radiologists regarding the potential  
363 malignancy of any unexplained soft tissue masses despite its local aspect. This could be  
364 included in the university education of medical students, lectures at local pediatric hospitals  
365 and emergency units, educational programs for surgeons and radiologists in conventions. The  
366 second step should be informing pediatricians and non-sarcoma specialists of the importance  
367 of sending any patient with a potential STS to a specialized “expert” center. Setting up a  
368 specific patient pathway for any superficial soft tissue masses is the optimal method to  
369 address this specific clinical situation. Using such a pathway, within one week, imaging is  
370 performed and analyzed by expert radiologists and an image-guided biopsy is immediately  
371 performed after TBM, before any treatment. When required, upfront or post-chemotherapy  
372 surgery is then planned and performed by a specialized surgeon trained in sarcoma surgery  
373 with the objective of R0 margins. This management allows less diagnostic wavering, accurate  
374 diagnosis and appropriate management.

375 **REFERENCES**

- 376 1. Brisse HJ, Orbach D, Klijanienko J. Soft tissue tumours: imaging strategy. *Pediatr Radiol.*  
377 2010;40(6):1019–28.
- 378 2. Les cancers en France, Les Données, INCa, édition 2015. 2016;
- 379 3. Ries LAG, Smith M, Gurney J, Linet M, Tamara T, Young J. Cancer incidence and survival  
380 among children and adolescents: United States SEER Program 1975-1995, National Cancer Institute,  
381 SEER Program. NIH Pub. 1999;99:4649.
- 382 4. Fletcher CDM. The evolving classification of soft tissue tumours - an update based on the new  
383 2013 WHO classification. *Histopathology.* 2014;64(1):2–11.
- 384 5. Papillard-Maréchal S, Brisse HJ, Pannier S, Ilharreborde B, Philippe-Chomette P, Irtan S, et  
385 al. Pseudotumoral soft tissue masses in children and adolescents. *Arch Pediatr.* 2015;22(1):14–23.
- 386 6. Casali PG, Abecassis N, Bauer S, Biagini R, Bielack S, Bonvalot S, et al. Soft tissue and  
387 visceral sarcomas: ESMO-EURACAN Clinical Practice Guidelines for diagnosis, treatment and  
388 follow-up. *Ann Oncol.* 2018;29(Supplement\_4):51–67.
- 389 7. Blay J-Y, Soibinet P, Penel N, Bompas E, Duffaud F, Stoeckle E, et al. Improved survival  
390 using specialized multidisciplinary board in sarcoma patients. *Ann Oncol.* 2017;28(11):2852–9.
- 391 8. Ray-Coquard I, Montesco MC, Coindre JM, Dei Tos AP, Lurkin A, Ranchère-Vince D, et al.  
392 Sarcoma: concordance between initial diagnosis and centralized expert review in a population-based  
393 study within three European regions. *Ann Oncol.* 2012;23(9):2442–9.
- 394 9. Blay J-Y, Honoré C, Stoeckle E, Meeus P, Jafari M, Gouin F, et al. Surgery in reference  
395 centers improves survival of sarcoma patients: a nationwide study. *Ann Oncol.* 2019;
- 396 10. Derbel O, Heudel PE, Crochet C, Meeus P, Vaz G, Biron P, et al. Survival impact of  
397 centralization and clinical guidelines for soft tissue sarcoma (A prospective and exhaustive population-  
398 based cohort). *PLoS ONE.* 2017;12(2):e0158406.
- 399 11. Chisholm JC, Merks JHM, Casanova M, Bisogno G, Orbach D, Gentet J-C, et al. Open-label,  
400 multicentre, randomised, phase II study of the EpSSG and the ITCC evaluating the addition of  
401 bevacizumab to chemotherapy in childhood and adolescent patients with metastatic soft tissue  
402 sarcoma (the BERNIE study). *Eur J Cancer.* 2017;83:177–84.
- 403 12. Zambo I, Veselý K. [WHO classification of tumours of soft tissue and bone 2013: the main  
404 changes compared to the 3rd edition]. *Cesk Patol.* 2014;50(2):64–70.
- 405 13. Donaldson SS, Draper GJ, Flamant F, Gerard-Marchant R, Mouriesse H, Newton WA, et al.  
406 Topography of childhood tumors: pediatric coding system. *Pediatr Hematol Oncol.* 1986;3(3):249–58.
- 407 14. Lawrence W, Anderson JR, Gehan EA, Maurer H. Pretreatment TNM staging of childhood  
408 rhabdomyosarcoma: a report of the Intergroup Rhabdomyosarcoma Study Group. Children's Cancer  
409 Study Group. Pediatric Oncology Group. *Cancer.* 1997;80(6):1165–70.
- 410 15. Bisogno G, Jenney M, Bergeron C, Gallego Melcón S, Ferrari A, Oberlin O, et al. Addition of

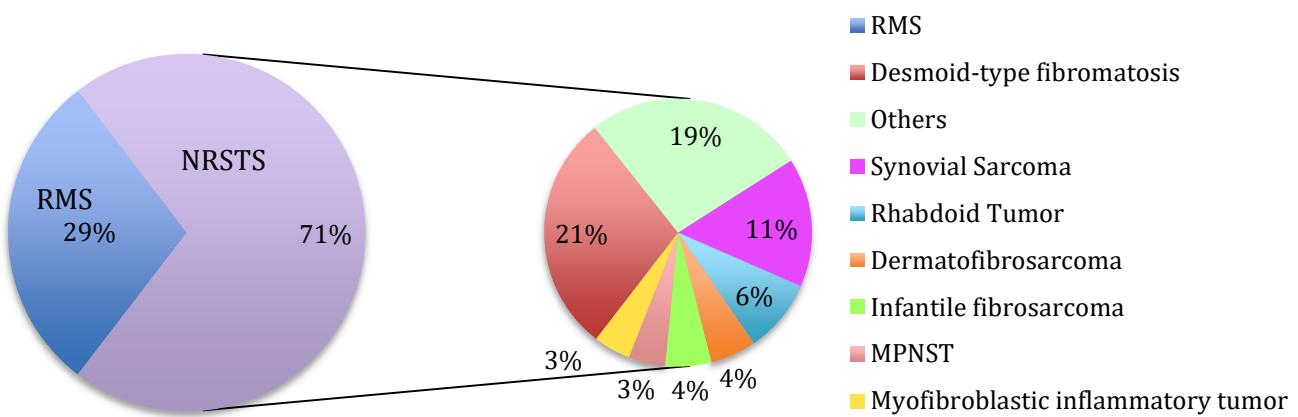
- 411 dose-intensified doxorubicin to standard chemotherapy for rhabdomyosarcoma (EpSSG RMS 2005): a  
412 multicentre, open-label, randomised controlled, phase 3 trial. Lancet Oncol. 2018;19(8):1061□71.
- 413 16. Ferrari A, Chi Y-Y, De Salvo GL, Orbach D, Brennan B, Randall RL, et al. Surgery alone is  
414 sufficient therapy for children and adolescents with low-risk synovial sarcoma: A joint analysis from  
415 the European paediatric soft tissue sarcoma Study Group and the Children's Oncology Group. Eur J  
416 Cancer. 2017;78:1□6.
- 417 17. Orbach D, Brennan B, Bisogno G, Van Noesel M, Minard-Colin V, Daragjati J, et al. The  
418 EpSSG NRSTS 2005 treatment protocol for desmoid-type fibromatosis in children: an international  
419 prospective case series. Lancet Child Adolesc Health. 2017;1(4):284□92.
- 420 18. Brennan B, De Salvo GL, Orbach D, De Paoli A, Kelsey A, Mudry P, et al. Outcome of  
421 extracranial malignant rhabdoid tumours in children registered in the European Paediatric Soft Tissue  
422 Sarcoma Study Group Non-Rhabdomyosarcoma Soft Tissue Sarcoma 2005 Study-EpSSG NRSTS  
423 2005. Eur J Cancer. 2016;60:69□82.
- 424 19. Hermanek P, Wittekind C. The pathologist and the residual tumor (R) classification. Pathol  
425 Res Pract. 1994;190(2):115□23.
- 426 20. Ray-Coquard I, Thiesse P, Ranchère-Vince D, Chauvin F, Bobin J-Y, Sunyach M-P, et al. Conformity to clinical practice guidelines, multidisciplinary management and outcome of treatment  
427 for soft tissue sarcomas. Ann Oncol. 2004;15(2):307□15.
- 429 21. Honoré C, Méeus P, Stoeckle E, Bonvalot S. Soft tissue sarcoma in France in 2015:  
430 Epidemiology, classification and organization of clinical care. J Visc Surg. 2015;152(4):223□30.
- 431 22. Gerrand CH, Wunder JS, Kandel RA, O'Sullivan B, Catton CN, Bell RS, et al. Classification  
432 of positive margins after resection of soft-tissue sarcoma of the limb predicts the risk of local  
433 recurrence. J Bone Joint Surg Br. 2001;83(8):1149□55.
- 434 23. Qureshi SS, Prabhu A, Bhagat M, Kembhavi S, Vora T, Chinnaswamy G, et al. Re-excision  
435 after unplanned resection of nonmetastatic nonrhabdomyosarcoma soft tissue sarcoma in children:  
436 Comparison with planned excision. J Pediatr Surg. 2017;52(8):1340□3.
- 437 24. Watson S, Perrin V, Guillemot D, Reynaud S, Coindre J-M, Karanian M, et al. Transcriptomic  
438 definition of molecular subgroups of small round cell sarcomas. J Pathol. 2018;245(1):29□40.
- 439 25. Antonescu CR, Owosho AA, Zhang L, Chen S, Deniz K, Huryn JM, et al. Sarcomas With  
440 CIC-rearrangements Are a Distinct Pathologic Entity With Aggressive Outcome: A Clinicopathologic  
441 and Molecular Study of 115 Cases. Am J Surg Pathol. 2017;41(7):941□9.
- 442 26. Hornick JL. Limited biopsies of soft tissue tumors: the contemporary role of  
443 immunohistochemistry and molecular diagnostics. Mod Pathol. 2019;
- 444 27. Smolle MA, Tunn P-U, Goldenitsch E, Posch F, Szakandera J, Bergovec M, et al. The  
445 Prognostic Impact of Unplanned Excisions in a Cohort of 728 Soft Tissue Sarcoma Patients: A  
446 Multicentre Study. Ann Surg Oncol. 2017;24(6):1596□605.
- 447 28. Kepka L, Suit HD, Goldberg SI, Rosenberg AE, Gebhardt MC, Hornicek FJ, et al. Results of  
448 radiation therapy performed after unplanned surgery (without re-excision) for soft tissue sarcomas. J

- 449 Surg Oncol. 2005;92(1):39□45.
- 450 29. Kasper B, Baumgarten C, Bonvalot S, Haas R, Haller F, Hohenberger P, et al. Management of  
451 sporadic desmoid-type fibromatosis: a European consensus approach based on patients' and  
452 professionals' expertise - a sarcoma patients EuroNet and European Organisation for Research and  
453 Treatment of Cancer/Soft Tissue and Bone Sarcoma Group initiative. Eur J Cancer.  
454 2015;51(2):127□36.
- 455 30. Lacour B, Clavel J. Epidemiological aspects of childhood cancer. Rev Prat.  
456 2014;64(9):1264□9.
- 457 31. Loeb DM, Thornton K, Shokek O. Pediatric soft tissue sarcomas. Surg Clin North Am.  
458 2008;88(3):615□27.
- 459 32. van der Graaf WTA, Orbach D, Judson IR, Ferrari A. Soft tissue sarcomas in adolescents and  
460 young adults: a comparison with their paediatric and adult counterparts. Lancet Oncol.  
461 2017;18(3):e166□75.
- 462 33. Tatencloux S, Mosseri V, Papillard-Maréchal S, Mesples B, Pellegrino B, Belloy M, et al.  
463 Care pathways before diagnosis in children and adolescents with malignancies. Bull Cancer.  
464 2017;104(2):128□38.
- 465 34. Ferrari A, Lo Vullo S, Giardiello D, Veneroni L, Magni C, Clerici CA, et al. The Sooner the  
466 Better? How Symptom Interval Correlates With Outcome in Children and Adolescents With Solid  
467 Tumors: Regression Tree Analysis of the Findings of a Prospective Study. Pediatr Blood Cancer.  
468 2016;63(3):479□85.
- 469 35. Ferrari A, Miceli R, Casanova M, Meazza C, Favini F, Luksch R, et al. The symptom interval  
470 in children and adolescents with soft tissue sarcomas. Cancer. 2010;116(1):177□83.



471

472 **Figure 1.** Flowchart of the study



473

474

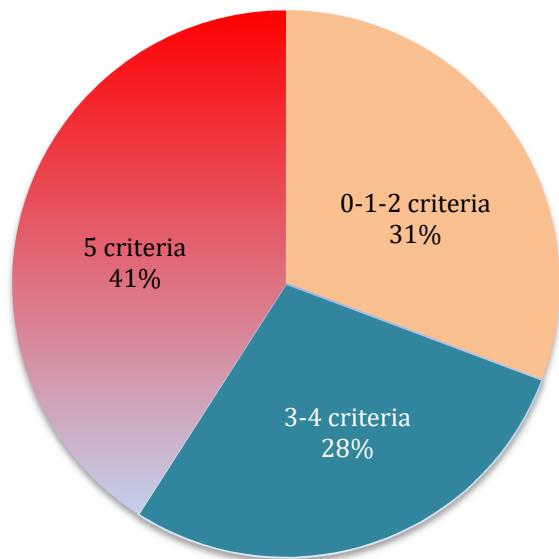
475 **Figure 2.** Histological distribution of localized sarcomas in the cohort

476

477 **Abbreviations:** RMS, rhabdomyosarcoma; NRSTS: non-rhabdomyosarcoma soft tissue sarcoma;

478 MPNST, Malignant Peripheral Nerve Sheath Tumor

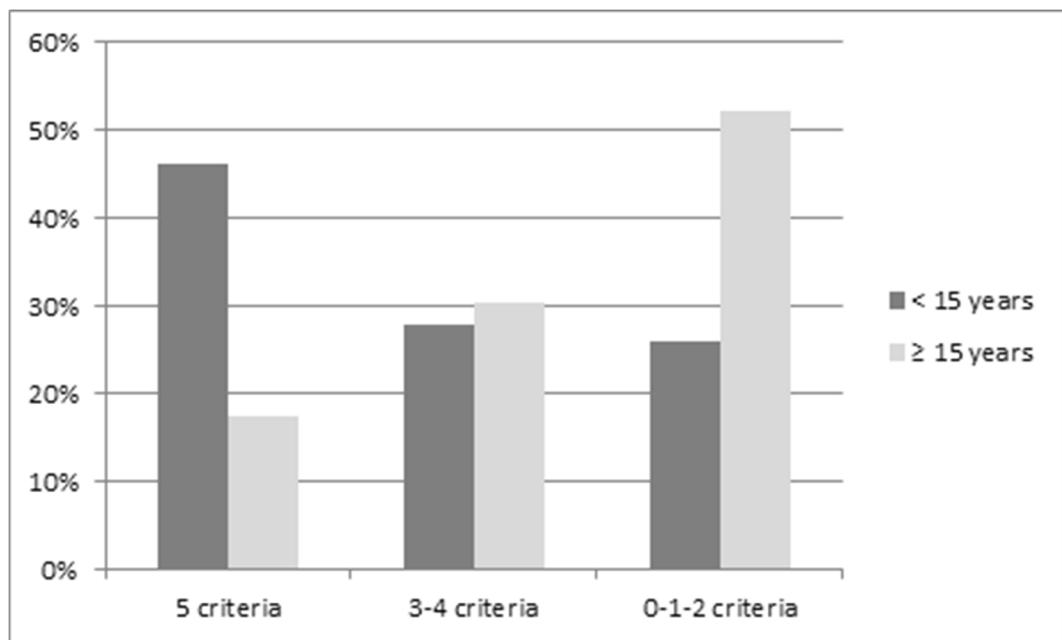
479



480

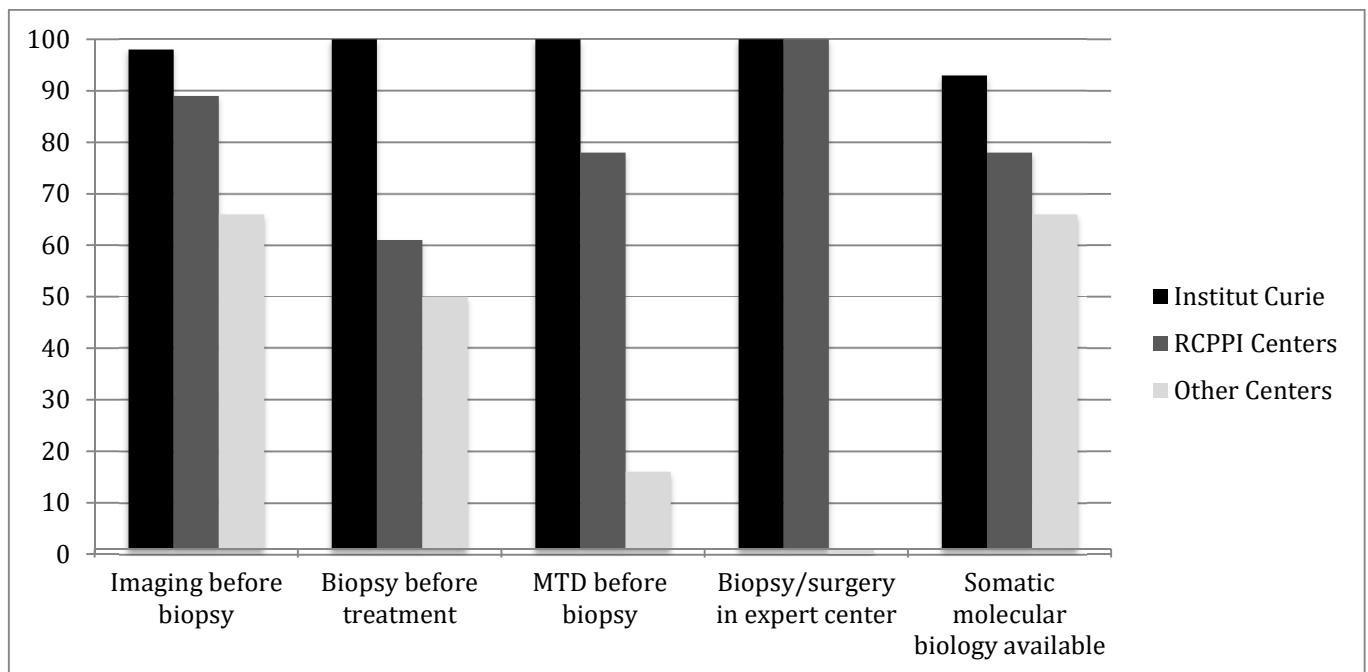
481 **Figure 3.** Number of compliance criteria present at the diagnosis of suspected sarcomas in children  
482

483



484  
485  
486

**Figure 4.** Percentage of compliance criteria according to patient's age



487

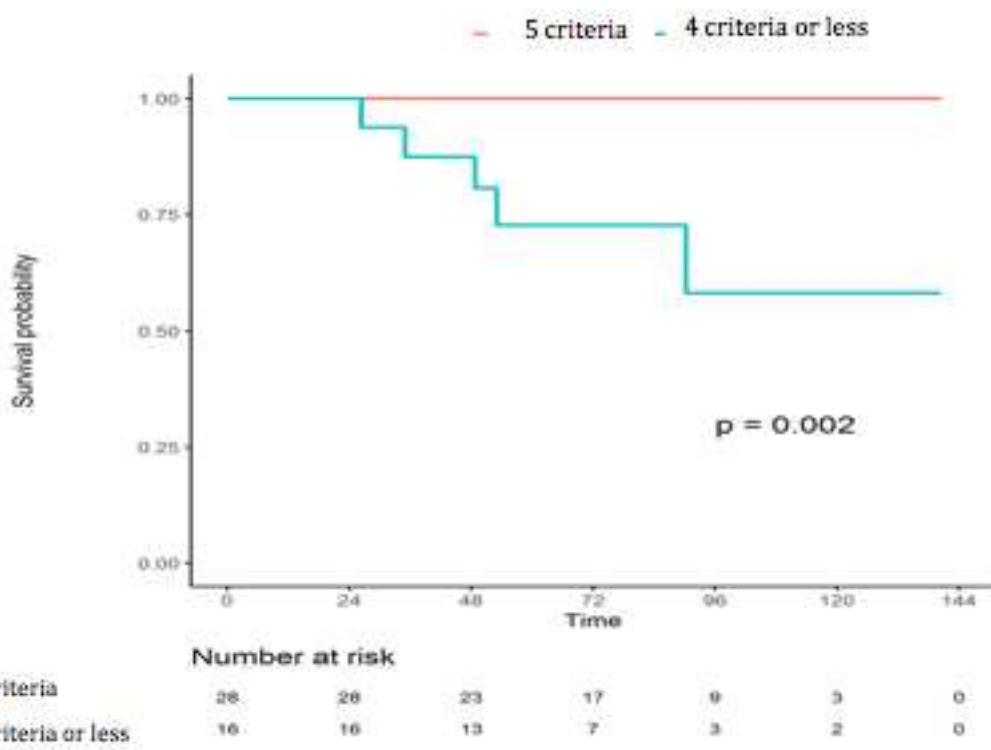
488

489 **Figure 5.** Compliance with optimal clinical practice guidelines according to the primary center where  
 490 patients were initially referred (results expressed in percentage of patients for each criterion)

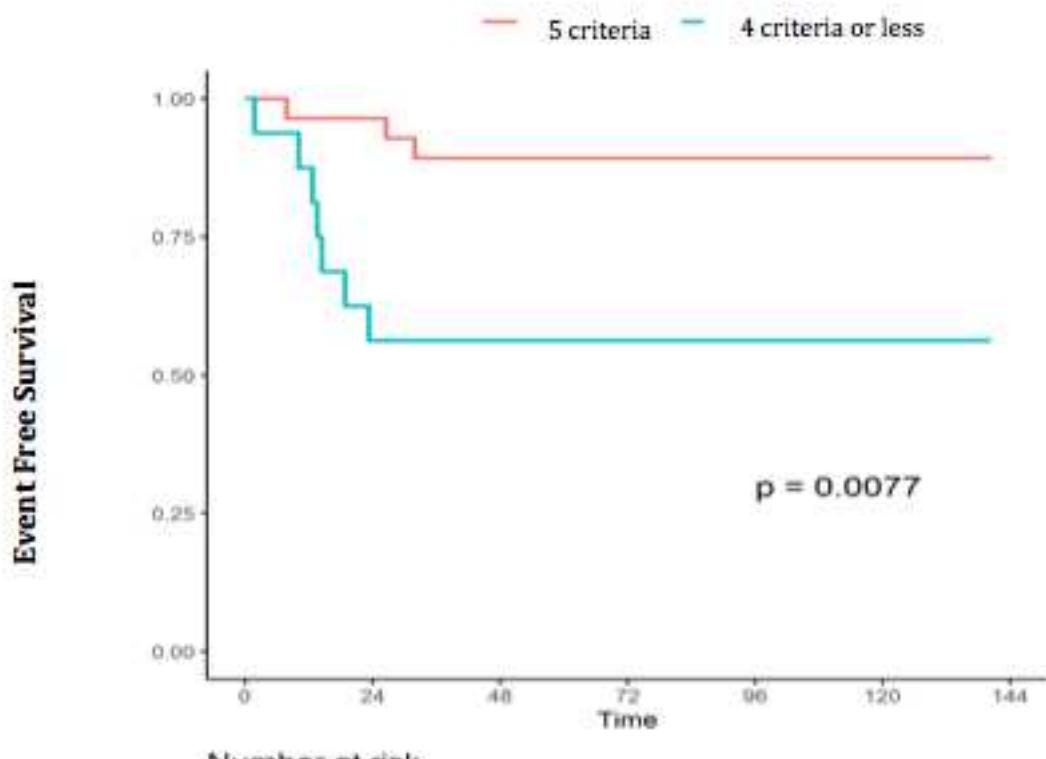
491

492

493



494  
495 **Figure 6.** Overall survivals according to CPG criteria fulfilled for all patients with small tumors  
496 ( $<5$  cm) at diagnosis. OS (in red) for patients with 5 criteria and (in blue) for  $\leq 4$  criteria.  
497  
498



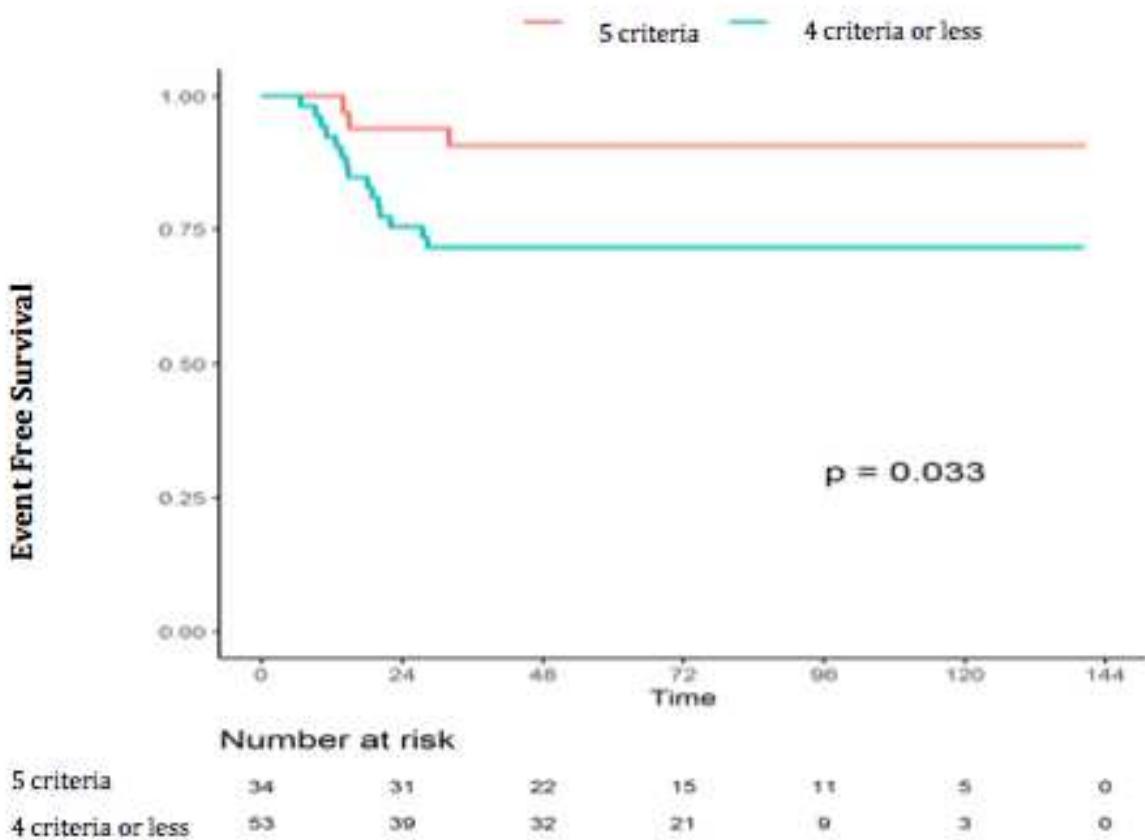
499

500

501 **Figure 7.** Event-free survivals according to CPG criteria fulfilled for all patients with small tumors  
502 ( $<5$  cm) at diagnosis. EFS (in red) for patients with 5 criteria and (in blue) for  $\leq 4$  criteria.

503

504



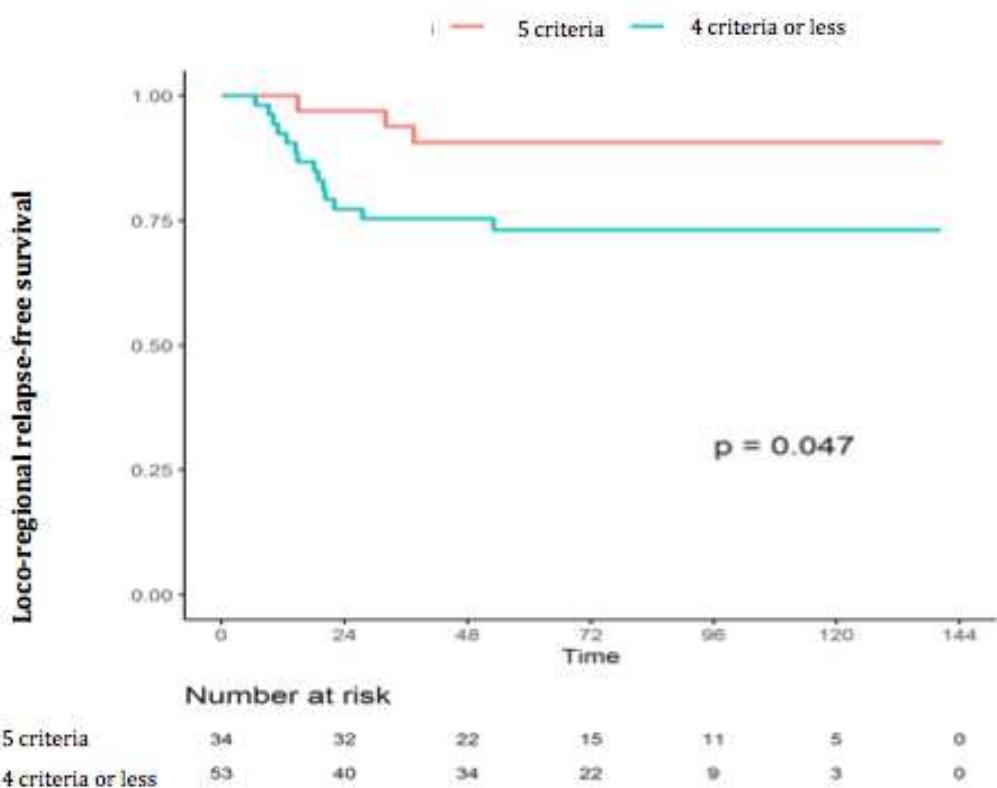
505

506

507 **Figure 8.** Event-free survival according to the total number of clinical practice guideline criteria  
508 fulfilled for patients with malignant sarcomas.

509

510



511

512

513

514 **Figure 9.** Loco-regional relapse-free survival according to the total number of optimal criteria for  
515 patients with malignant sarcoma.

516

**Table I.** Patient and tumor population characteristics

Characteristics	Number of patients	%
<b>Total</b>	<b>127</b>	<b>100</b>
<b>Patient characteristics</b>		
<i>Gender:</i>		
<b>Male</b>	78	61
<b>Female</b>	49	39
<i>Age:</i>		
< 10 y	65	51
≥ 10 y	62	49
<b>Initial tumoral characteristics</b>		
<i>Histology:</i>		
<b>NRSTS</b>	90	71
<b>Malignant tumor</b>	50	
<b>Intermediate tumor</b>	40	
<b>RMS</b>	37	29
<i>Tumor's primary site:</i>		
<b>Limb</b>	64	50
<b>Head and neck</b>	36	28
<b>Chest wall</b>	11	9
<b>Abdominal wall</b>	6	5
<b>Paratesticular</b>	5	4
<b>Perineal</b>	1	1
<b>Other</b>	4	3
<i>Tumor size:</i>		
<b>≤ 5 cm</b>	76	60

<b>&gt; 5 cm</b>	44	35
------------------	----	----

<b>Unknown</b>	7	5
----------------	---	---

***Clinical nodal enlargement:***

<b>N0</b>	97	77
-----------	----	----

<b>N1</b>	12	9
-----------	----	---

<b>Nx</b>	18	14
-----------	----	----

**Imaging performed before diagnosis:**

<b>Ultrasound</b>	90	71
-------------------	----	----

<b>CT scan</b>	37	29
----------------	----	----

<b>MRI</b>	96	76
------------	----	----

<b>No CT or MRI</b>	17	13
---------------------	----	----

<b>No CT, MRI or ultrasound</b>	6	5
---------------------------------	---	---

**Treatment:**

***Surgery***

<b>At diagnosis</b>	59	46
---------------------	----	----

<b>Overall</b>	100	79
----------------	-----	----

***Chemotherapy***

	78	61
--	----	----

***Radiotherapy***

<b>Associated with surgery</b>	41	32
--------------------------------	----	----

<b>Overall</b>	52	41
----------------	----	----

---

519

520      **Abbreviations:** y, years; RMS, rhabdomyosarcoma; NRSTS: non-rhabdomyosarcoma soft tissue  
521      sarcoma; MRI, magnetic resonance imaging.

522

523 **Table II.** Compliance with criteria according to the initial referring center

	<b>Expert centers (RCPPI + Institut Curie)</b>	<b>Other general centers</b>	<b>P value</b>
		<b>50 cases</b>	
	<b>77 cases</b>		
<b>Imaging before biopsy</b>	72	33	p < 0.0001
<b>Biopsy before treatment</b>	63	25	p < 0.0001
<b>MTD before biopsy</b>	69	8	p < 0.0001
<b>Somatic molecular biology available</b>	66	33	p = 0.009

524

525 **Abbreviations:** MTD, Multidisciplinary Tumor Board, RCPPI *réunion de concertation*526 *pluridisciplinaire Pédiatrique Interrégionale*

527

528 **Table III.** Number of new surgeries according to the number of optimal criteria present at diagnosis

	Total number of optimal criteria			Total
	5	3-4	0-1-2	
<b>Number of reoperations</b>	3/52 cases	9/36 cases	22/39 cases	<b>34 cases</b>
<b>% of reoperations</b>	6.0%	25.0%	56.4%	<b>27.2%</b>
529				p < 0.0001

530

531 **Table IV.** Overall Survival after stratification according to risk factors

532

	<b>Presence of 5 criteria</b>	<b>4 criteria or less</b>	<b>P-Value</b>
<b>Tumor &lt; 5 cm</b>	100% (95% IC100-100)	72.7 (95% IC 52.9-100.0)	0.002
<b>Tumor &gt; 5 cm</b>	81% (95% IC 63.2-100.0)	89.9% (95% IC 81.8-98.8)	0.48
<b>Malignant Tumor</b>	93.6% (95% IC 85.5-100.0)	79.5% (95% IC 68.9-91.8)	0.11
<b>Intermediate Tumor</b>	92.3% (95% IC (78.9-100.0)	100 % (95% IC 100.0-100.0)	0.58
<b>Age &lt; 10 y</b>	91.5% (95% IC 80.7-100.0)	83.2% (95%IC 71.8-96.5)	0.21
<b>Age &gt; 10 y</b>	95.2% (95% IC (86.6-100.0)	87.2% (95% IC 76.0-100.0)	0.35

533

534

535 **Table V.** Event-Free Survival after stratification according to risk factors  
536

	<b>5 criteria</b>	<b>4 criteria or less</b>	<b>P-Value</b>
<b>Tumor &lt; 5 cm</b>	89.3% (95% IC 78.5-100.0)	56.2% (95% IC 36.5-86.7)	0.0077
<b>Tumor &gt; 5 cm</b>	71.1% (95% IC 54-93.6)	81.2% (95% IC -71.3-92.4)	0.32
<b>Malignant Tumors</b>	90.8% (95% IC 81.4-100.0)	71.6% (95% IC 60.4-84.9)	0.033
<b>Intermediate Tumors</b>	66.7% (95% IC 48.1-92.4)	81.3% (95% IC 66.4-99.7)	0.088
<b>Age &lt; 10 y</b>	81.5% (95% IC 68.1-97.5)	68.4% (95%IC 55.1-84.9)	0.21
<b>Age &gt; 10 y</b>	83.1% (95% IC 69.3-99.7)	80.7% (95% IC 68.7-94.6)	0.86

537

538 **Table VI. Loco-regional Relapse-Free Survival after stratification**

	<b>5 criteria</b>	<b>4 criteria or less</b>	<b>P-Value</b>
<b>Tumor &lt; 5 cm</b>	89.3% (95% IC 78.5-100.0)	61.1% (95% IC 40.8-91.4)	0.012
<b>Tumor &gt; 5 cm</b>	69.6% (95% IC 51.7-93.6)	85% (95% IC -75.9-95.1)	0.17
<b>Malignant Tumor</b>	90.6% (95% IC 81.0-100.0)	73.1% (95% IC 62.0-86.3)	0.047
<b>Intermediate Tumor</b>	66.7% (95% IC 48.1-92.4)	90.5% (95% IC 78.8-100.0)	0.088
<b>Age &lt; 10 y</b>	81.5% (95% IC 68.1-97.5)	73.7% (95% IC 60.9-89.1)	0.31

539