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

4
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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%, ≤ 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 ≤ 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%; ≤ 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.

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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 ≤ 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 ≤ 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 ≤ 2 , $P= 0.265$) or for LRRFS (82% when 5 criteria vs. 76.7% when 3-4 and 79.2%
251 when ≤ 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 (± 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

272 optimal CPGs are frequently reported in the literature over the years, the diagnostic pathway
273 for patients with STS often does not follow these recommendations, even in adults (20).
274 Adequate CPGs recommend multidisciplinary management for any soft tissue tumor as soon
275 as the clinical and radiological presentation is not consistent with a typical benign lesion (6).
276 However, patients are initially frequently managed outside reference centers (20). Notably, in
277 our experience, 39% of pediatric patients were initially not managed in specialized centers. In
278 France, *NetSarc* was created in 2009 to improve and homogenize the management of French
279 patients with sarcomas, by building a large clinical national adult network including 28
280 reference centers sharing a common database (21). It gathers clinical and pathological data
281 from patients treated for soft tissue and visceral sarcomas, which is then discussed in sarcoma
282 multidisciplinary committees. After 10 years, it was demonstrated that patients initially
283 managed in expert *Netsarc* centers had a higher rate of compliance with CPGs, a better
284 LRRFS as well as higher rates of complete R0 surgery and less need for reoperations (5.5%
285 when a *NetSarc* MTD was held before surgery vs. 15.3% after, in a series of 12,528 patients;
286 $p < 0.0001$)(7)(9). The quality of initial resection is a recognized strong prognostic factor in
287 soft-tissue sarcomas: R2 and R1 margins are associated with more relapses despite any further
288 oncological management (22). Unplanned excisions (so-called “whoops” procedures) are
289 associated with more local relapses despite further treatments (23). International Guidelines
290 therefore recommend referring every patient with a soft tissue tumor (deep-seated tumors or
291 superficial masses larger than 3 to 5 cm) to a specialized center before any treatment.
292 However, the diagnostic course and its impact on survival in children are still unknown. In
293 our experience, about one-third of patients get unplanned surgery without prior histological
294 diagnosis, whereas a precise biopathological diagnosis is mandatory to define the most
295 appropriate treatment (24)(25). Molecular biology is especially mandatory nowadays in order
296 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**

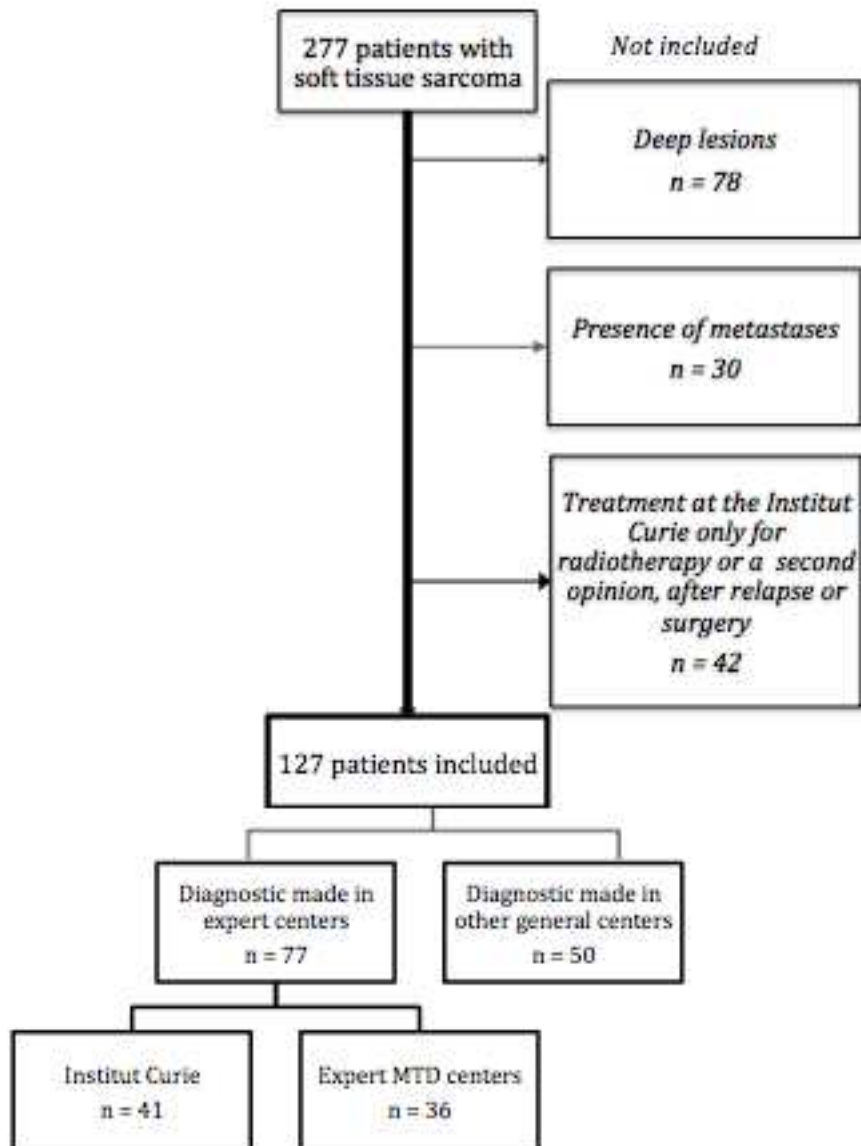
360
361 To improve compliance, we need to first improve the knowledge of pediatricians,
362 general practitioners, surgeons, dermatologists and radiologists regarding the potential
363 malignancy of any unexplained soft tissue masses despite its local aspect. This could be
364 included in the university 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.

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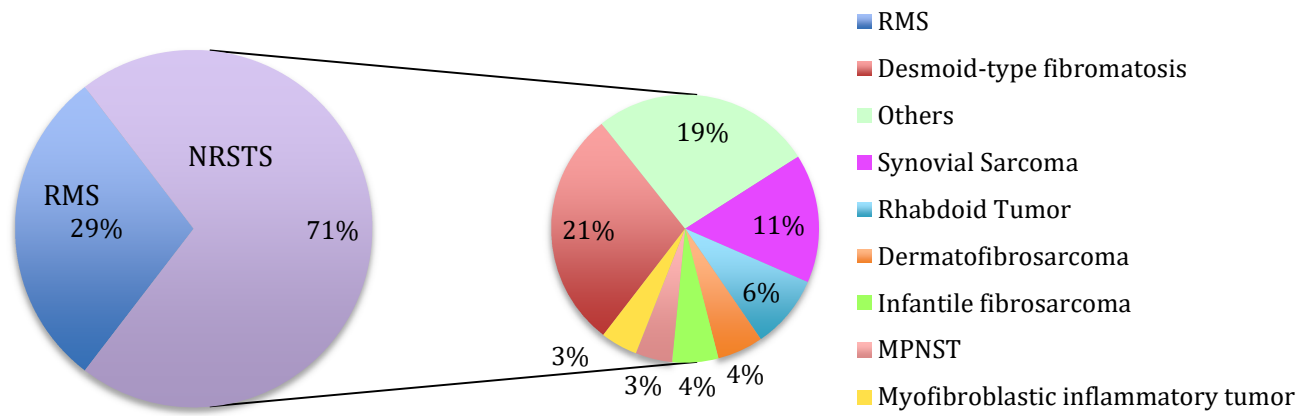
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472 **Figure 1.** Flowchart of the study



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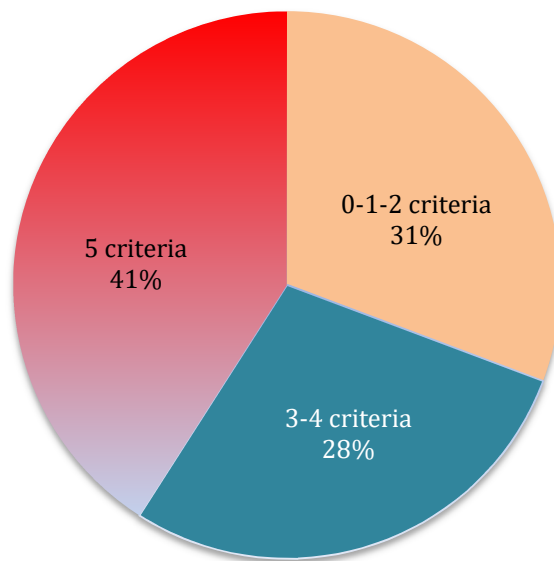
475 **Figure 2.** Histological distribution of localized sarcomas in the cohort

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

478 MPNST, Malignant Peripheral Nerve Sheath Tumor

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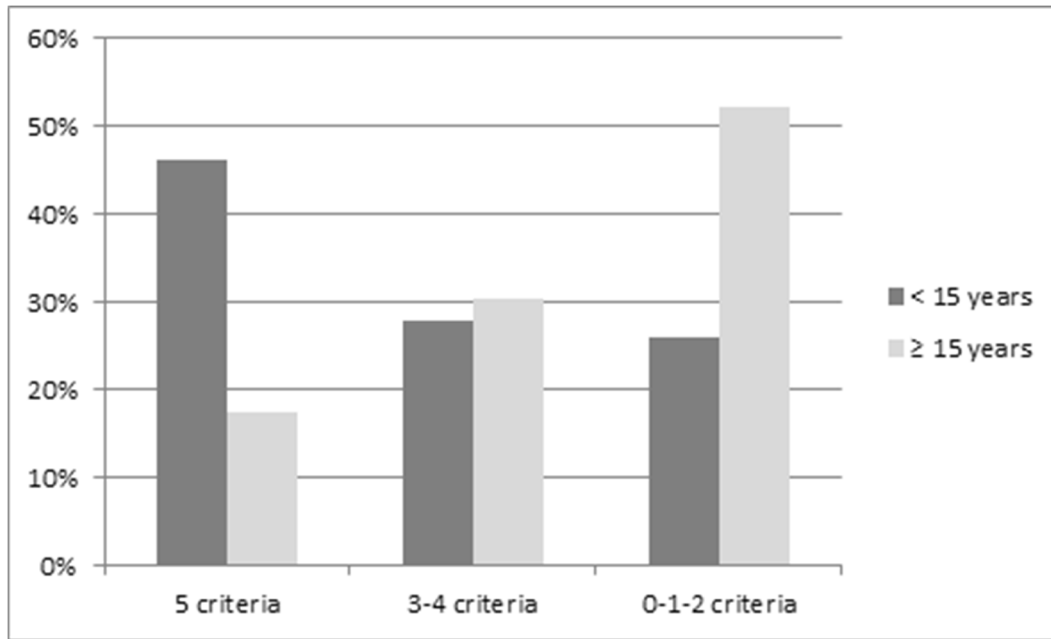


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481 **Figure 3.** Number of compliance criteria present at the diagnosis of suspected sarcomas in children

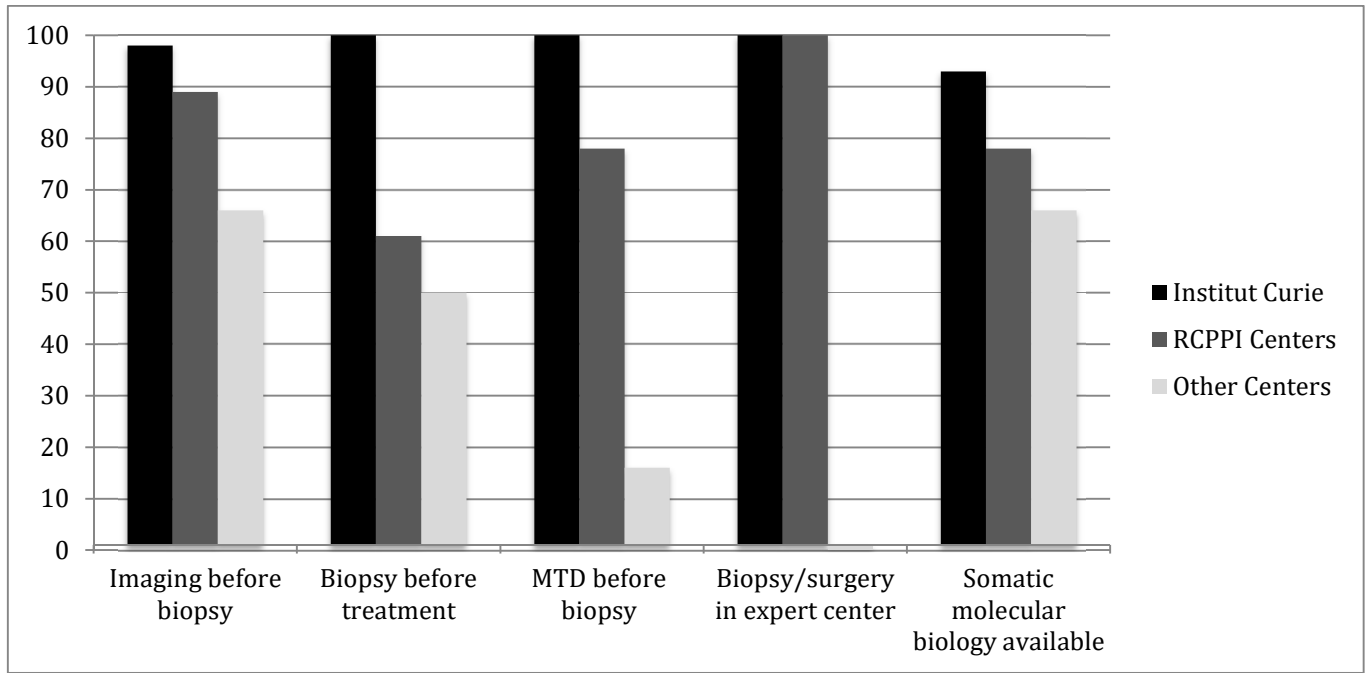
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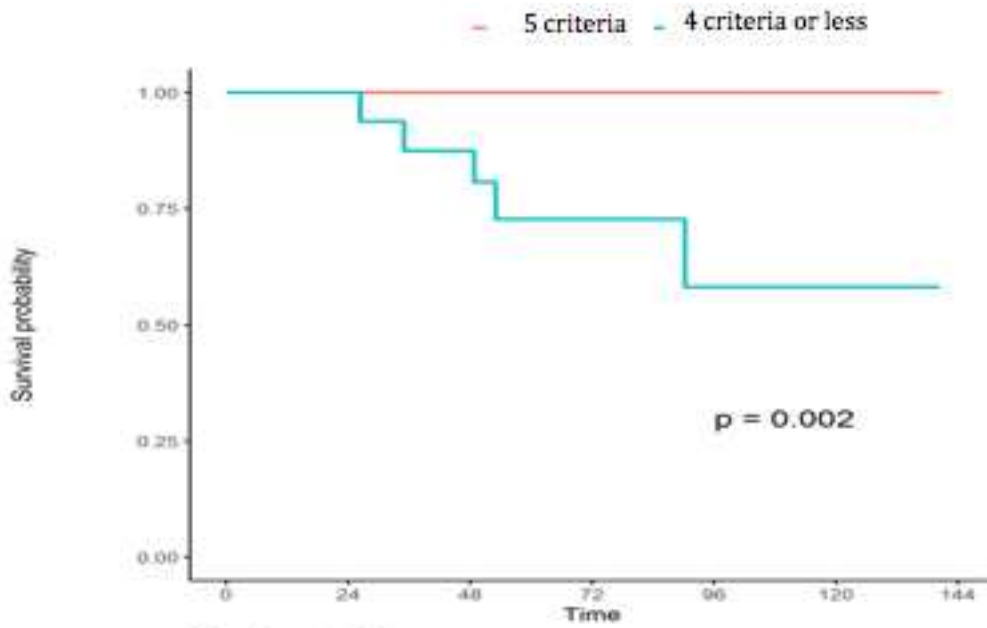
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Figure 4. Percentage of compliance criteria according to patient's age



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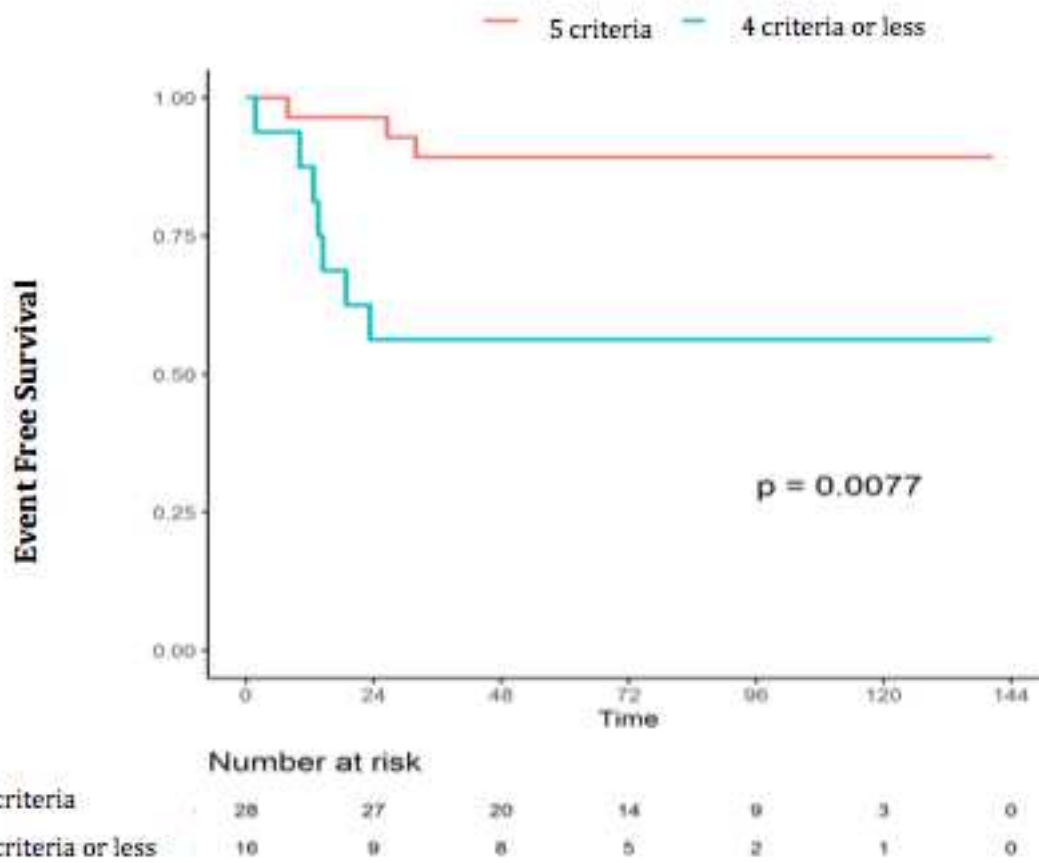
Figure 5. Compliance with optimal clinical practice guidelines according to the primary center where patients were initially referred (results expressed in percentage of patients for each criterion)



	Number at risk						
	0	24	48	72	96	120	144
5 criteria	28	28	23	17	9	3	0
4 criteria or less	16	16	13	7	3	2	0

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Figure 6. Overall survivals according to CPG criteria fulfilled for all patients with small tumors (<5 cm) at diagnosis. OS (in red) for patients with 5 criteria and (in blue) for ≤ 4 criteria.



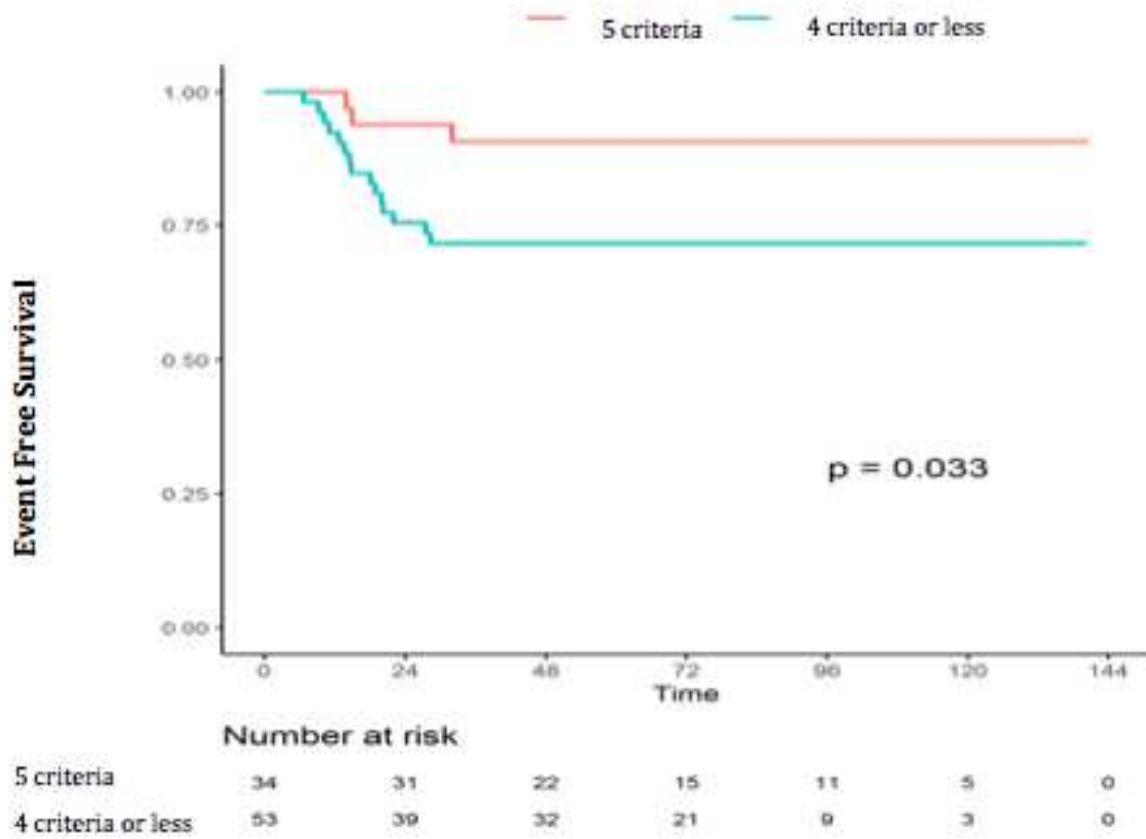
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501 **Figure 7.** Event-free survivals according to CPG criteria fulfilled for all patients with small tumors
 502 (<5 cm) at diagnosis. EFS (in red) for patients with 5 criteria and (in blue) for ≤ 4 criteria.

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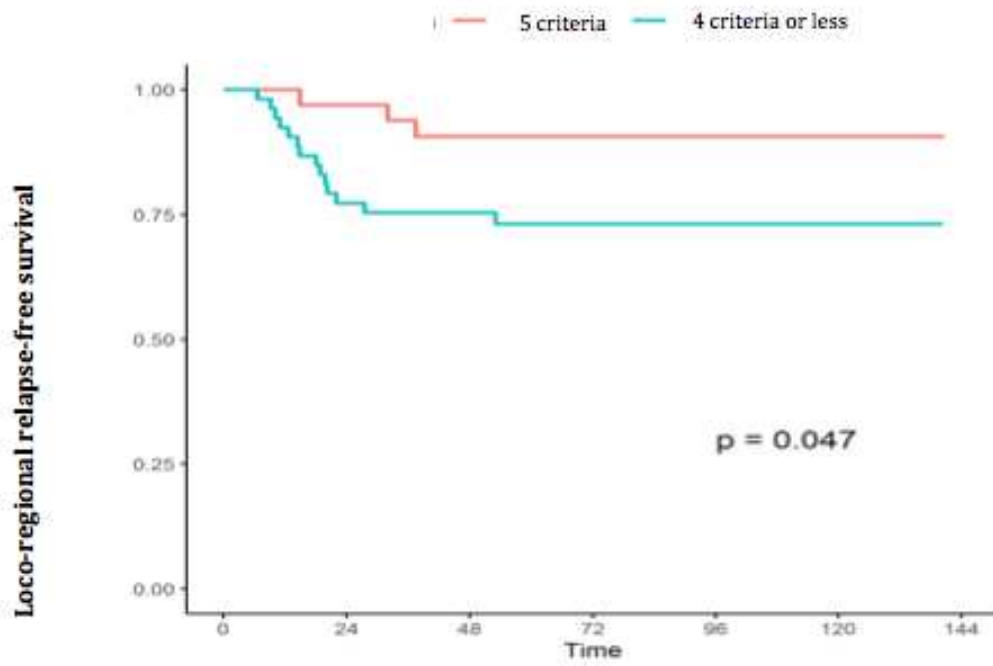
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507 **Figure 8.** Event- free survival according to the total number of clinical practice guideline criteria
 508 fulfilled for patients with malignant sarcomas.

509

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	0	24	48	72	96	120	144
5 criteria	34	32	22	15	11	5	0
4 criteria or less	53	40	34	22	9	3	0

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513

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

515 patients with malignant sarcoma.

516

517 **Table I.** Patient and tumor population characteristics
518

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

> 5 cm	44	35
Unknown	7	5
<i>Clinical nodal enlargement:</i>		
N0	97	77
N1	12	9
Nx	18	14
Imaging performed before diagnosis:		
Ultrasound	90	71
CT scan	37	29
MRI	96	76
No CT or MRI	17	13
No CT, MRI or ultrasound	6	5
Treatment:		
<i>Surgery</i>		
At diagnosis	59	46
Overall	100	79
<i>Chemotherapy</i>	78	61
<i>Radiotherapy</i>		
Associated with surgery	41	32
Overall	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

	Expert centers (RCPPI + Institut Curie) 77 cases	Other general centers 50 cases	P value
Imaging before biopsy	72	33	p < 0.0001
Biopsy before treatment	63	25	p < 0.0001
MTD before biopsy	69	8	p < 0.0001
Somatic molecular biology available	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	p < 0.0001
	5	3-4	0-1-2		
Number of reoperations	3/52 cases	9/36 cases	22/39 cases	34 cases	
% of reoperations	6.0%	25.0%	56.4%	27.2%	

529

530

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

532

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

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

	5 criteria	4 criteria or less	P-Value
Tumor < 5 cm	89.3% (95% IC 78.5-100.0)	61.1% (95% IC 40.8-91.4)	0.012
Tumor > 5 cm	69.6% (95% IC 51.7-93.6)	85% (95% IC -75.9-95.1)	0.17
Malignant Tumor	90.6% (95% IC81.0-100.0)	73.1% (95% IC 62.0-86.3)	0.047
Intermediate Tumor	66.7% (95% IC 48.1-92.4)	90.5% (95% IC 78.8-100.0)	0.088
Age < 10 y	81.5% (95% IC 68.1-97.5)	73.7% (95%IC 60.9-89.1)	0.31

539