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Clinical management of adolescents and young adults suffering from sarcoma in the French Rhône-Alpes region: A prospective exhaustive cohort with 10 years follow up

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1 Clinical management of adolescents and young adults suffering from
2 sarcoma in the French Rhône-Alpes region: a prospective exhaustive
3 cohort with 10 years follow up.

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47

1 ABBREVIATIONS

AG	Anderson-Gill model
ARCERRA	Childhood Cancer Registry of Rhone-Alpes
AYA	Adolescents and young adults
CPGs	Clinical practice guidelines
CRISAP-RA	Centre de Regroupement Informatique et Statistique en Anatomie Pathologique in the Rhône-Alpes region
ESMO	European Society of Medical Oncology
GSF-GETO	French Sarcoma Group
INCa	French national cancer Institute
MTB	Multidisciplinary tumour board
OS	Overall survival
PWP	Prentice-Williams-Peterson model
RA	Rhone-Alpes region
RFS	Relapse free survival
STS	Soft Tissue Sarcoma
WLW	Wei, Lin and Weissfeld model

ABSTRACT

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Introduction: Survival of adolescents and young adults (AYA) with sarcoma is lower than in younger patients. The objective of this study was to describe the regional healthcare circuits, the differences in the management between adult, paediatric and mixed units and to assess the prognostic impact of compliance with clinical practice guidelines (CPGs) on overall survival (OS) and on relapse free survival (RFS).

Materials and methods: Retrospective analysis of the management and long term follow-up of all 13 - 25 year old patients with a sarcoma diagnosed in the Rhône-Alpes area between 2000 and 2005.

Results: 140 patients satisfied inclusion criteria and were selected. The majority of 13-25 year old patients were treated in paediatric units. Joint management resulted in a higher rate of discussion in multidisciplinary tumour board, inclusion in clinical trials, and fertility preservation. Non-compliance with guidelines was observed in 65% of cases Overall compliance was not reported to correlate to survival. Compliance of radiotherapy with CPG's seemed associated with a better prognosis for OS (HR = 0.20, 95% CI = [0.10 – 0.40]; p<0.0001) and RFS (HR = 0.18, 95% CI = [0.09 – 0.37; p < 0.0001) as well as compliance of surgery for OS (HR = 0.43, 95% CI = [0.23 - 0.81]; p = 0.01). Multivariate Cox regression analysis revealed other independent predictors of OS like age at diagnosis, stage and histological subtype.

Conclusions: Management of AYA in joint units seems to improve the quality of care. Compliance of surgery and radiotherapy with CGP's seems to improve survival.

79 INTRODUCTION

80
81 To date, the specific features of adolescents and young adults (AYA) with cancer
82 have widely been identified and described (1). Nevertheless, data from the literature
83 reveal that this specific population benefits less from medical progress than the
84 paediatric or adult populations (2–4). Several parameters might explain these
85 discrepancies such as tumour biology, factors specifically related to patients,
86 hormonal modifications, psychological aspects (5). While more than 90% of
87 paediatric patients are enrolled in clinical trials, only 20% patients are involved
88 between 15 and 19, and 8% patients between 20 and 24 (6). Furthermore, disparities
89 within the AYA population are observed in terms of survival rates according to the
90 type of management they benefited from (7–9).

91 Adolescent patients are treated either in paediatric or in adults units and the currently
92 available data remain unclear regarding both treatment approaches and patient
93 benefit (10–13).

94 We designed this study to contribute to establish specific recommendations for AYA
95 management.

96 The first objective was to evaluate the differences in medical management between
97 adult, paediatric and mixed units and to assess the compliance with clinical practice
98 guidelines (CPGs) in each institution. The second objective was to assess the
99 prognostic impact of compliance with CPGs on overall survival (OS) and relapse free
100 survival (RFS) adjusting for previously established prognostic factors. The third
101 objective was to perform a modelling of recurrent events and a joint frailty modelling.

102

2 METHODS

103 **2.1 Study population**

104

105 This observational study took place retrospectively in the French Rhone-Alpes region
106 (RA) including 3 university hospitals, 1 regional cancer centre, 27 general hospitals
107 and 42 private structures. Since RA represents 10% of the national population, 200
108 cases of AYA cancers were expected each year among the 15-24 year old patients,
109 including 22 cases of sarcomas (11%) (14).

110 Data from 13 to 25 year old patients with a primary diagnosis of a localized or
111 metastatic sarcoma according to the 2002 WHO definition between Jan 1st, 2000 and
112 Dec 31st, 2005 was collected and analysed.

113 Patients with a diagnosis of relapse or a non-sarcoma diagnosis after second
114 histological review were excluded.

115

116 **2.2 Measurement of compliance with clinical practice guidelines**

117

118 The CPGs selected for analysis of conformity were those on-going during the period
119 2000-2005 including paediatric/adult regional and national or international (ESMO)
120 guidelines (15–17). All steps of management from initial diagnosis to follow up were
121 evaluated following technics of medical audit previously published (18,19). An overall
122 compliance was determined if all sequences were consistent but one deviation in one
123 sequence generated a "non-compliant" management

124 Compliance with CPGs was evaluated by the same 2 specialists (both a medical
125 adult oncologist and a paediatric oncologist) for all patient records in an attempt to
126 avoid inter-observer reproducibility bias. There was no disagreement between the
127 specialists.

128 **2.3 Data collection**

129
130 Patients were identified by extracting of diagnoses from the pathologists' laboratories
131 of the Centre de Regroupement Informatique et Statistique en Anatomie
132 Pathologique (CRISAP) Rhône-Alpes and from the Regional Childhood Cancer
133 Registry (ARCERRA) (20). The project received a favourable opinion from the
134 Commission Nationale de l'Informatique et des Libertés (CNIL). All data relative to
135 medical history and treatments administered were collected by monitoring the
136 medical files in all units. Patient follow-up was done for 10 years.

137 **2.4 Statistics**

138 All statistical analyses were carried out using Stata software, version 15.

139 **2.4.1 Data management, descriptive and bivariate analysis**

140
141 Baseline characteristics were presented as simple proportions for categorical
142 variables. Mean, standard deviation, median and range were used to describe
143 continuous variables.

144 Bivariate analyses were performed using χ^2 or Fisher exact test, for categorical
145 variables and Student t test or Kruskal-Wallis test were used to compare means.

146 OS and RFS were defined as main outcomes. OS was defined as time from
147 histological diagnosis to death from any cause. RFS was defined as time from
148 histological diagnosis to first relapse, progression or death from any cause,
149 whichever occurred first.

150 Kaplan-Meier method was used to estimate the overall survival time and Log rank
151 test to compare survival curves.

152 $p < .05$ was set as the statistically significant threshold in comparison between
153 groups.

154 **2.4.2 Modelling approaches**

155 **2.4.2.1 Non recurrent events analysis**

156
157 OS and RFS analysis were performed. Univariate and multivariate Cox proportional
158 hazard regression, with robust variance estimate were used.

159 Proportional hazard assumption was checked using tests based on Schoenfeld
160 residuals. Loglinearity was checked using fractional polynomials (21).

161 A Royston-Parmar model was used when proportional hazard assumption was
162 violated.

163 Concordance was assessed via Harrell's C and Gonen and Heller's K concordance
164 coefficients.

165 **2.4.2.2 Recurrent events analysis**

166
167 The first three relapses were taken into account.

168 The extended Cox models (22) were used to model recurrent events within a subject.

169 The models were: the counting process model (Anderson-Gill model or AG) and the
170 conditional model (Prentice-Williams-Peterson model or PWP).

171 Use of Wei, Lin and Weissfeld (WLW) marginal model for recurrent events is
172 controversial. We nevertheless implemented it as exploratory tool.

173 The robust variance estimator of Lin and Wei was used together with these Cox
174 extended models to avoid inflation of type I error due to multiple observations per
175 individual.

176 **2.4.2.3 Joint frailty survival analysis**

177
178 We used a joint frailty model, originally proposed by Liu et al. (23) to jointly model
179 recurrent events and death. Recurrences and survival were modelled in conjunction
180 with a Weibull model and an exponential model respectively.

2.4.3 Model selection and goodness of fit

The log likelihood (LL), Akaike information criterion (AIC) and Bayesian information criterion (BIC) were used to compare the goodness of fit of the models.

2.4.4 Missing data

Missing values of covariates were excluded from all statistical analysis. Multiple imputation was not performed.

3 RESULTS

220 cases were initially collected in the RA via the CRISAP and declared by 25 pathological laboratories (including 14 private ones). 145 patients matching the inclusion criteria were included in the study of which 140 were selected for management and compliance description. 122 cases were finally assessable for OS and RFS in the multivariate analysis ([Figure 1](#)).

The characteristics of all selected patients, according to the unit of management, are described in [Table 1](#).

The median follow-up time, estimated by the reverse Kaplan-Meier based method was 11.44 years (95% CI = [9.95 – 11.75]).

Concerning the 140 patients' outcome, 47 (33.6%) relapsed after the initial treatment sequence. Of these 47 patients, 18 (12.8%) were alive at the time of the last news and 29 (20.7%) died of their cancer.

20 (14.2%) patients progressed during the initial treatment sequence. Of these, 2 (1.4%) were cured by salvage treatment. The remaining 18 (12.9%) patients died of their cancer.

207 73 (52.1%) patients responded to the initial treatment sequence and did not relapse.
208 Of these, 2 (1.4%) died of another cancer, 1 (0.7%) died of haemorrhagic stroke and
209 1 (0.7%) of undetermined cause.

210 **3.1 Management**

211 The management of all 140 patients was assessed (Table 2). 30.7% were treated in
212 adult units, 56.4% in paediatric and 12.8% in mixed.

213 74% of cases were discussed in multidisciplinary tumour board (MTB) in the adult
214 units, 87% in the paediatric units and 100% in the mixed units ($p = 0.026$). The rate of
215 inclusions in clinical trials was 21% in the adult units, 34% in the paediatric units and
216 56% with joint management ($p = 0.03$). Finally, fertility preservation was achieved in
217 37% of patients treated in adult sectors versus 59% in paediatric sectors, and 61% in
218 mixed units ($p = 0.046$)

219 **3.2 Compliance with clinical practice guidelines**

220
221 The analysis of compliance is described in Table 3. Overall compliance with CGPs
222 from initial diagnosis to follow up was only 35%. It was not significantly impacted by
223 the type of care structure since it reached 37% in the adult units, 28% in the
224 paediatric structures and 44% in the mixed ones ($p = 0.415$).

225 Among the compliance of the different sequences of management with CPGs, only
226 the compliance of the initial diagnosis appeared statistically higher in the mixed units
227 (83% vs 53% in adult units and 79% in paediatric structures; $p = 0.007$). The
228 conformity of the other steps of management was not significantly impacted by the
229 type of care structure.

230

231 **3.3 Overall Survival**

232
233 In the global AYA population (n = 145), OS at 5 years and 10 years was 62% (95%
234 CI = [53 – 70] and 57% (95%CI = [48 – 65]) respectively. The median OS was 14.24
235 years (Figure 2).

236 In univariate analysis, we found a statistically significant prognostic impact of age at
237 diagnosis (HR = 1.09, 95% CI = [1.02 – 1.17]; p = 0.01), stage (HR = 4.70, 95% CI =
238 [2.14 – 10.28]; p<0.0001) and compliance of radiotherapy (HR = 0.24, 95% CI = [0.14
239 – 0.41]; p<0.0001).

240 The following factors appeared at the limit of significance: grade (HR = 0.16, 95%CI =
241 [0.02 – 1.35]; p = 0.09) and at least one discussion in MTB (HR = 2.84, 95%CI =
242 [0.97 – 8.35]; p = 0.06). Compliance of surgery (HR = 0.66, 95%CI = [0.31 – 1.42]; p
243 = 0.29) and chemotherapy (HR = 0.77, 95%CI = [0.45 – 1.31]; p = 0.33) were also
244 considered for the multivariate analysis because of their clinical relevance.

245 In multivariate analysis (Table 4) by adjusting for the previously selected factors in
246 univariate analysis, there was a highly significant prognostic impact of compliance of
247 radiotherapy (HR = 0.20, 95% CI = [0.10 – 0.40]; p<0.0001) and compliance of
248 surgery (HR = 0.43, 95% CI = [0.23 - 0.81]; p = 0.01) (Figure 4).

249 Multivariate Cox regression analysis revealed that other independent predictors of
250 OS included stage (HR = 2.89, 95%CI = [1.08 – 7.78]; p =0.04) and age at diagnosis
251 (HR = 1.10, 95%CI = [1.01 – 1.20]. p = 0.04). Histological sub-type was at the limit of
252 statistical significance (HR = 1.96, 95%CI = [0,90 – 4.28]; p= 0.09).

253

254 **3.4 Relapse free survival**

255

256 In the global AYA population (n = 145), RFS at 5 years and 10 years was 59% (95%
257 CI = [50 – 66]) and 48% (95% CI = [39 – 57]) respectively. The median RFS was 9.13
258 years (Figure 3).

259 The RFS multivariate analysis relied on the relevant factors previously highlighted in
260 OS multivariate analysis.

261 In this RFS multivariate analysis (Table 5), compliance of radiotherapy was
262 consistently identified as an independent prognostic factor (HR = 0.18, 95% CI =
263 [0.09 – 0.37]; p<0.0001). Compliance of surgery was at the limit of statistical
264 significance (HR = 0.40, 95% CI = [0.40 – 1.08]; p = 0.096) as well as age (HR =
265 1.10, 95%CI = [0.99 – 1.21]; p = 0.08) and histological subtype (HR = 1.89, 95%CI =
266 [0.92 – 3.90], p = 0.085)

267 Multivariate Cox regression analysis revealed stage as another independent
268 predictors of RFS (HR = 2.47, 95% CI = [1.07 – 5.73]; p = 0.03)

269

270 **3.5 Modelling of recurrent events**

271 **3.5.1 Recurrent events analysis**

272

273 The different modellings of recurrent events used to analyze the risk of recurrence
274 are visible in Table 6 and Table 7

275 The prognostic impact of compliance of radiotherapy was found in several models:
276 WLW and PWP (time from previous event).

277 The metastatic stage was prognostic in most models: AG and PWP (time from entry
278 and time from previous event).

279 **3.5.2 Joint frailty survival analysis**

280

281 The results of the joint frailty analysis are shown in Table 8.

282 Age at diagnosis, metastatic stage and compliance of radiotherapy were significantly
283 correlated to the risk of relapse.

284 Metastatic stage, histological sub-type and compliance of radiotherapy were
285 significantly correlated to the risk of death.

286 Age at diagnosis, compliance of chemotherapy and compliance of surgery were at
287 the limit of the statistical significance.

288

289

4 DISCUSSION

290 This cohort of primary sarcoma in AYA patients is the first prospective exhaustive
291 series reported in literature. One of the strength of this study is the data quality of
292 cases reported at the regional level due to reliable sources of archives from
293 pathologists and regional registry, insuring exhaustive information. Survival data in
294 this series are comparable to data published in the 14-25 year old population
295 between 2000 and 2008 reporting a 50% 5 years-OS for bone sarcomas and 70% for
296 soft tissue sarcomas (14).

297 In France in the 2000's, AYA with cancer were treated either in paediatric or in
298 adult oncology units depending on some random (or not) factors, like age, pathology,
299 care sectors, and geographical sites of care management. While patients younger
300 than 15 mostly benefit from care management in paediatric unit from specialized
301 centres, data is less clear for patients over 15 and their care management is more
302 heterogeneous (24).

303 In this study, 58% of the 13-25 year old patients were managed in one of the three
304 regional paediatric oncology units. The rest of the population was managed in
305 multiple adult oncology units in a total of 27 different referenced departments. Mixed
306 units represent 13% of the regional oncology organisation during the study period

307 (2000 – 2005). This was a particularly innovative approach since the AYA issue was
308 rarely considered during the study period (2000-2005) and AYA units didn't exist in
309 France at that time. Desandes et al. reported 68% of patients with cancer aged from
310 15 to 19 between 2006 and 2007 were treated in adult units and described no care
311 management in mixed units.

312 82% of cases were discussed in MTB. The proportions are slightly different in
313 paediatric or adult care management (87% and 74% respectively), but interestingly
314 rises to 100% for patients treated in mixed complementary paediatric and adult
315 structures ($p=0.026$). Several studies have shown the benefit of multidisciplinary
316 approaches in oncology and the possible benefits on survival (18,19).

317 The inclusion rate in clinical trials decreases with age up to a maximum of 30%
318 for the 15-19 bracket versus less than 5% for older patients (12,24,25). Although the
319 enrolment into clinical trials never formally demonstrated any benefit in terms of
320 survival, it clearly improves the care management, and allows therapeutic advances.
321 Despite the existence of European cooperative trials for both children and adults
322 patients, we observe a deficit of participation of young adults. While more than 90%
323 of paediatric patients are enrolled, only 20% are between the age of 15 and 19, and
324 8% between 20 and 24. As reported in the literature (26), in this study, the rate of
325 inclusion is lower when care management is provided in adult units (21%) versus
326 paediatric (34%). Interestingly, the rate rises up to 56% when a joint unit combining
327 paediatric and adult approach is performed ($p = 0.03$) which argues for the benefits of
328 such collaboration.

329 We also reported a higher rate of fertility preservation proposals in mixed and
330 in paediatric sectors compared to adult ones.

331 According to various studies, reconciliation of the medical practices and their
332 impact on patient outcomes could be linked (27,28). It was also shown that
333 compliance with the CPGs could influence the prognosis of patients (29). In this
334 series, compliance to CPGs was one of the selected criteria to evaluate the quality of
335 care. The overall compliance rate for all the therapeutic sequence was very low with
336 35%. These figures are comparable to the data reported by Ray-Coquard et al. or
337 Heudel et al., in adults with STS (34%) (18,19).

338 In this study, neither overall compliance nor mixed management appear to be
339 prognostic determinants of OS or RFS.

340 By contrast, the compliance of radiotherapy seems highly associated with a better
341 prognosis in this specific population (in terms of OS and risk of relapse). This
342 emphasizes the radio-sensitivity of some sarcomas in this age group and the
343 importance of respecting the timing and doses of radiotherapy. It could also be
344 informative to investigate the dose-response relationship in these patients, compared
345 to older and younger patients respectively.

346 Moreover, the compliance of surgery seems significantly correlated to OS with an
347 impact on RFS at the limit of statistical significance. A favourable prognostic impact
348 on the risk of death was also found in the joint frailty analysis. This confirms the
349 crucial interest of a well-managed surgery in sarcoma pathology, especially in AYAs.

350 Interestingly, in several models age increases the death and relapse risk in a linear
351 manner, which could be in favour of biological differences between patients' tumours
352 according to their age or a different sensitivity to the proposed treatments.

353 Thus, here we show a strong and scientifically plausible association between
354 compliance of radiotherapy/ surgery and a reduced probability of relapse and death.

355 Even if the causality cannot be formally established in this study, the persistence of

356 the association in the different models used tends to correlate these two concepts.
357 This relationship has already been reported in the literature in larger studies and should be
358 further investigated (13,30).

359 In addition, we report a benefit from mixed units in terms of discussion in MTB,
360 inclusion in therapeutic trials and fertility preservation. This benefit must be tempered
361 due to the limited number of mixed management over the period considered ($n = 4$)
362 and further studies seem required to confirm this trend. Since 2012, the National
363 Cancer Institute in France (INCa) has recommended such joint management
364 concerning AYA, which could facilitate the implementation of this type of study.

365 Finally, limitations of this study reside in its retrospective design, its small
366 sample size and the regional nature of this research which could reduce the external
367 validity of the findings. Nevertheless it is a comprehensive exhaustive study that
368 reliably reflects practices in the Rhône-Alpes region.

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5 CONCLUSION

371 Joint management seems to improve the care quality for AYA by increasing the
372 fertility preservation rate, the number of discussions in MTB and inclusion in
373 therapeutic trials.

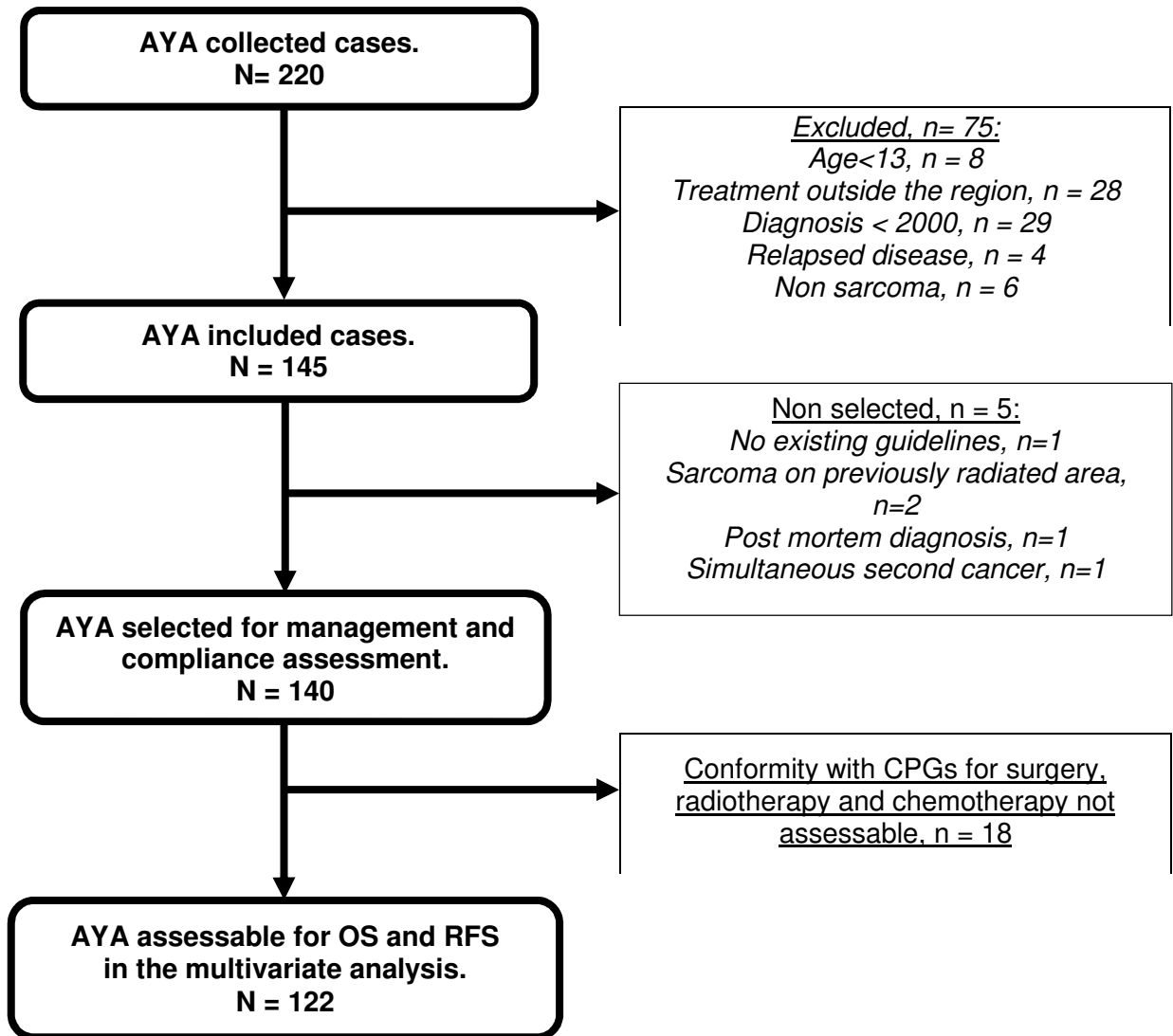
374 The compliance of radiotherapy and surgery seems highly correlated to OS and risk
375 of relapse.

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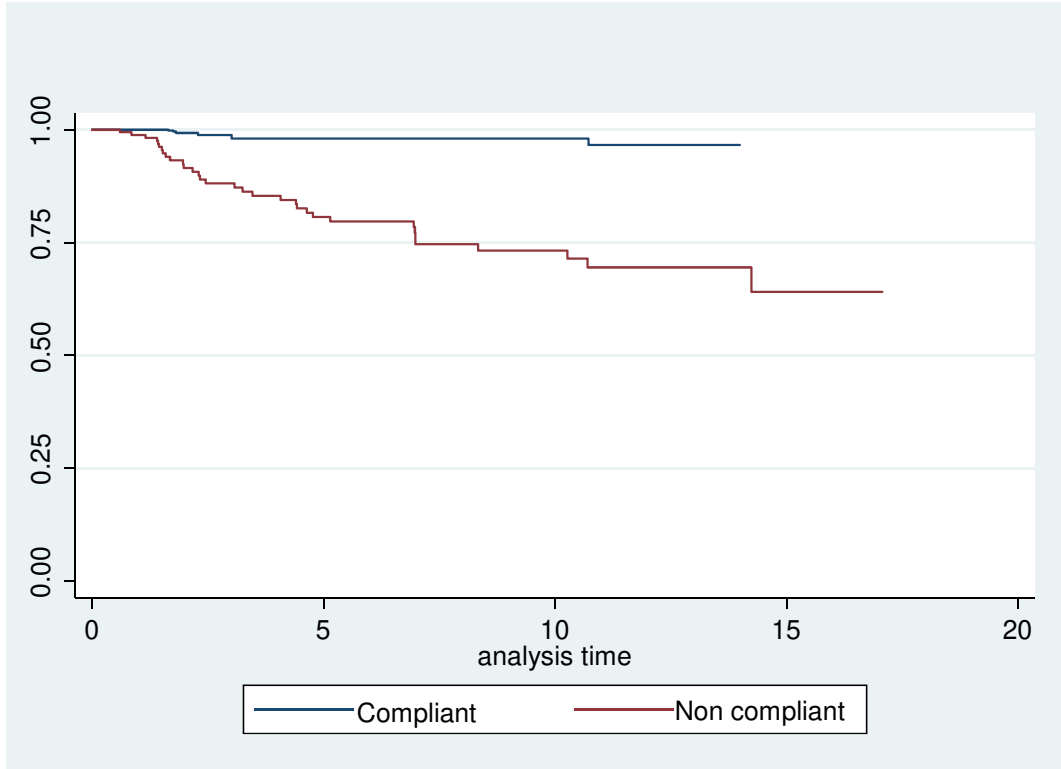
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6 FIGURES

Figure 1: Patient selection



402 **Figure 4: OS according to the compliance of surgery with CPGs, adjusted for**
403 **age, compliance of radiotherapy with CPGs, histological sub-type and stage**
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7 TABLES

411 **Table 1: characteristics of patients by units of management (n = 140)**

Characteristics	Adult n=43	Pediatric n=79	Mixed n=18	Total N	Chi ² -Test
Sex					
Male	27 (63%)	52 (66%)	9 (50%)	88	p=0.45
Female	16 (37%)	27 (34%)	9(50%)	52	
Age					
13-17	6 (14%)	62 (79%)	3 (17%)	71	p< 0.001
18-25	37 (86%)	17 (21%)	15 (83%)	69	
Type of sarcoma					
Soft tissue/Visceral	24 (56%)	27 (34%)	5 (28%)	56	p=0.035
Bone	19 (44%)	52 (66%)	13 (72%)	84	
Histology					
Osteosarcoma	9 (21%)	33 (42%)	5 (27%)	47	p< 0.001
Ewing sarcoma	7 (16%)	20 (25%)	9 (50%)	36	
Rhabdomyosarcoma	1 (2%)	11 (14%)	2 (11%)	14	
Unclassified sarcoma	5 (12%)	4 (5%)	1 (6%)	10	
Chondrosarcoma	4 (9%)	5 (6%)	-	9	
Synovial sarcoma	6 (14%)	3 (4%)	-	9	
Other	11 (26%)	3 (4%)	1 (6%)	15	
Localization					
Member	28 (65%)	49 (62%)	9 (50%)	86	p=0.53
Other	15 (35%)	30 (38%)	9 (50%)	54	
Grade					
1	9 (21%)	2 (3%)	-	11	p<0.001
2	7 (16%)	7 (9%)	-	14	
3	15 (35%)	44 (55%)	14 (78%)	73	
Unknown	12 (28%)	26 (33%)	4 (22%)	42	
Metastases at diagnosis					
Yes	10 (23%)	21 (27%)	5 (28%)	36	p=0.90
No	33 (77%)	58 (73%)	13 (72%)	104	

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Table 2: characteristics of management, treatment and response to treatment (n = 140)

Management		Adult n=43	Pediatric n=79	Mixed n=18	Chi ² -Test
First diagnosis					p=0.429
	Family doctor	10 (23%)	16 (20%)	8 (44%)	
	General hospital	12 (28%)	25 (32%)	2 (11%)	
	University hospital	9 (21%)	17 (22%)	4 (22%)	
	Other	12 (28%)	21 (26%)	4 (22%)	
Structure					p<0.001
	University hospital	15 (36%)	25 (32%)	2 (11%)	
	General hospital	8 (18%)	1 (1%)	-	
	Cancer Center	12 (28%)	47 (60%)	15 (83%)	
	Other	8 (18%)	6 (8%)	1 (6%)	
Histology before management					p<0.001
	Yes	24 (56%)	68 (86%)	16 (89%)	
	No	19 (44%)	11 (14%)	2 (11%)	
At least one MTB decision					p=0.026
	yes	32 (74%)	69 (87%)	18 (100%)	
	No	11 (26%)	10 (13%)	-	
Median number	median (min-max)	1 (0-9)	3 (0-9)	3 (1-7)	
Management					p=0.03
	Within clinical trial	9 (21%)	27 (34%)	10 (56%)	
	Dedicated registry	8 (19%)	40 (51%)	3 (16%)	
	No	26 (60%)	12 (15%)	5 (28%)	
Fertility preservation		16 (37%)	47 (59%)	11 (61%)	P=0.046
Description Treatments					P = 0.10
	Surgery	40 (93)	65 (83)	15 (83)	
	Chemotherapy	16 (37)	61 (77)	14 (77)	
	Radiation therapy	16 (37)	28 (35)	10 (55)	
Response end therapies					p=0.629
	Complete response	35 (82%)	59 (75%)	13 (72%)	
	Partial response	1 (2%)	5 (6%)	-	
	Stable disease	1 (2%)	3 (4%)	2 (11%)	
	Progressive disease	4 (9%)	10 (13%)	3 (17%)	
	Not evaluable	2 (5%)	2 (2%)	-	
Relapse or progressive disease					p=0.216
	Yes	22 (51%)	32 (41%)	11 (61%)	
	No	21 (49%)	47 (59%)	7 (39%)	
Site of relapse					p=0.027
	Local	12 (60%)	5 (16%)	4 (36%)	
	Metastatic	6 (30%)	19 (61%)	6 (55%)	
	Both	2 (10%)	7 (23%)	1 (9%)	
	Undetermined	2	1	-	
Status of patient					p=0.385
	Alive	23 (54%)	48 (61%)	11 (61%)	
	Death	16 (37%)	29 (37%)	7 (39%)	
	Lost of follow up	4 (9%)	2 (2%)	-	

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Table 3: compliance with Guidelines according to sequence of management (n=140)

Sequence of management	Conform	Non Conform	Not applicable	Chi ² -Test
Initial diagnosis	100 (71.4%)	40 (28.6%)	-	p=0.007
Paediatric	62 (79%)	17 (21%)	-	
Adult	23 (53%)	20 (47%)	-	
Mixed	15 (83%)	3 (17%)	-	
Histology	127 (91%)	13 (9%)	-	p=0.734
Paediatric	73 (92%)	6 (8%)	-	
Adult	38 (88%)	5 (12%)	-	
Mixed	16 (89%)	2 (11%)	-	
Initial surgery	92 (66%)	33 (24%)	15 (10%)	p=0.28
Paediatric	56 (71%)	15 (19%)	8 (10%)	
Adult	24 (56%)	15 (35%)	4 (9%)	
Mixed	12 (66%)	3 (17%)	3 (17%)	
Revision (2d) Surgery	16 (11%)	19 (14%)	105 (75%)	p=0.161
Paediatric	2 (3%)	13 (16%)	64 (81%)	
Adult	11 (26%)	5 (11%)	27 (63%)	
Mixed	3 (17%)	1 (5%)	14 (78%)	
Chemotherapy	82 (59%)	54 (38%)	4 (3%)	p=0.284
Paediatric	42 (53%)	36 (46%)	1 (1%)	
Adult	29 (67%)	12 (28%)	2 (5%)	
Mixed	11 (61%)	6 (33%)	1 (6%)	
Radiotherapy	111 (79%)	11 (8%)	18 (13%)	p=0.616
Paediatric	66 (84%)	5 (6%)	8 (10%)	
Adult	31 (72%)	4 (9%)	8 (19%)	
Mixed	14 (78%)	2 (11%)	2 (11%)	
Surveillance	95 (68%)	11 (8%)	34 (24%)	p=0.200
Paediatric	55 (70%)	5 (6%)	19 (24%)	
Adult	29 (67%)	6 (14%)	8 (19%)	
Mixed	11 (61%)	-	7 (39%)	
All management	49 (35%)	91 (65%)	-	p=0.415
Paediatric	29 (37%)	50 (63%)	-	
Adult	12 (28%)	31 (72%)	-	
Mixed	8 (44%)	10 (56%)	-	

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425 **Table 4: multivariate Cox regression model for OS**

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variable	HR	[95% CI]	p
Age at diagnosis	1.10	1.01 – 1.20	0.04
Histology (bone)	1.96	0.90 – 4.28	0.09
Stage			
2	0.80	0.29 – 2.26	0.68
3	0.92	0.30 – 2.80	0.88
4	2.89	1.08 – 7.78	0.04
Grade 3	0.96	0.67 – 1.36	0.78
Discussion in MTB	1.39	0.54 – 3.57	0.49
Compliance of radiotherapy	0.20	0.10 – 0.40	<0.0001
Compliance of surgery	0.43	0.23 – 0.81	0.01
Compliance of chemotherapy	0.62	0.32 – 1.20	0.15

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8 ANNEXE SECTION

Figure 2: OS analysis of AYA patients with sarcoma using Kaplan Meier method

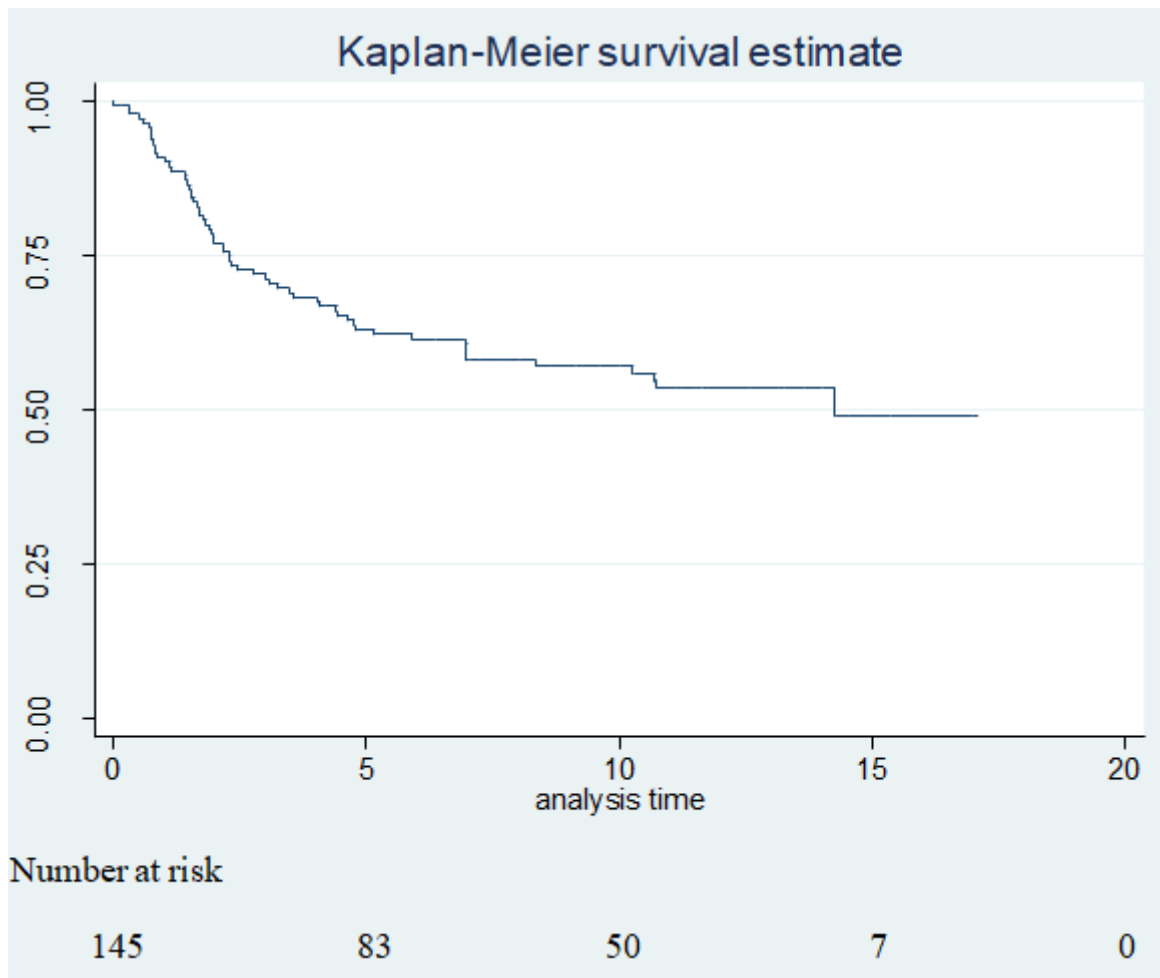


Figure 3: RFS analysis of AYA patients with sarcoma using Kaplan Meier method

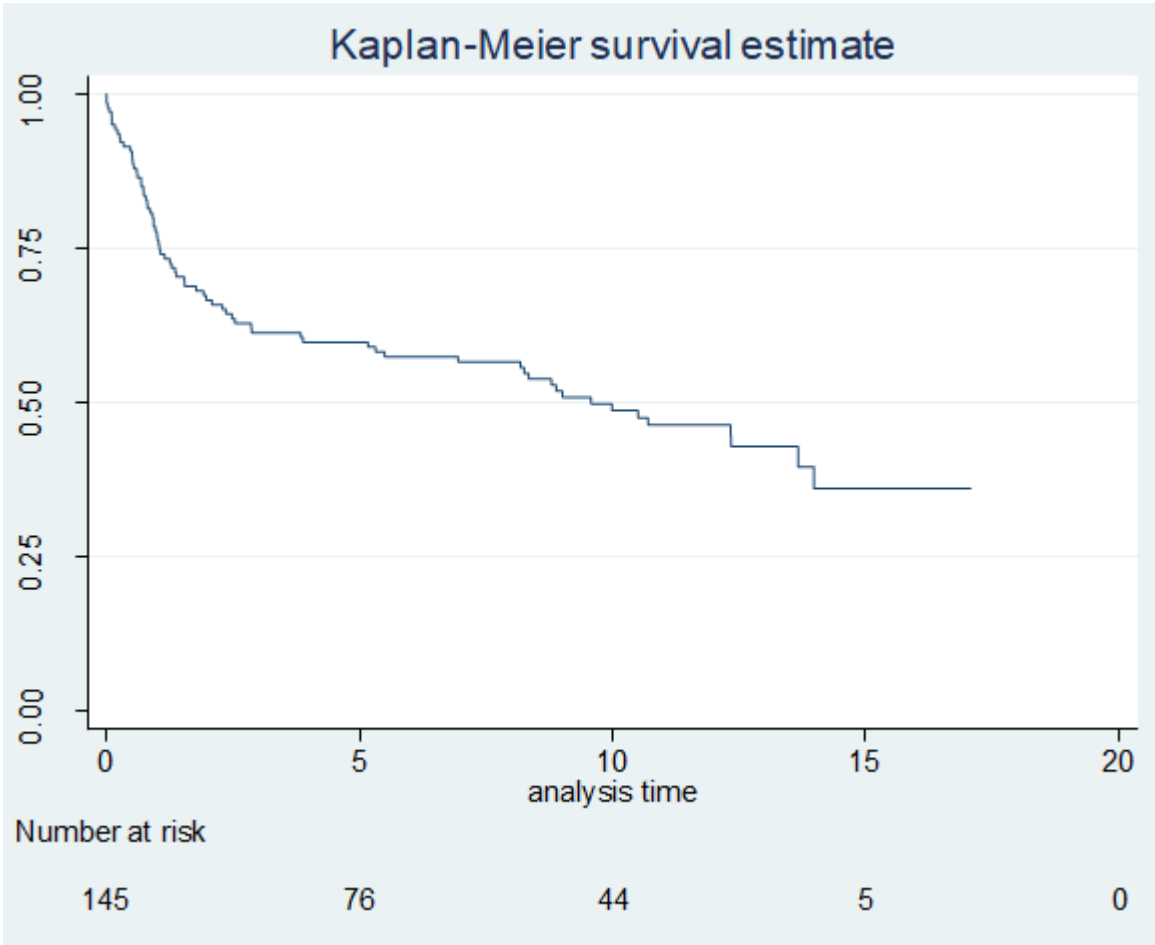


Table 5: multivariate Cox regression model for RFS

variable	HR	[95% CI]	p
Age at diagnosis	1.10	0.99 – 1.21	0.08
Histology (bone)	1.89	0.92 – 3.90	0.085
Stage			
2	0.88	0.40 – 1.93	0.75
3	0.73	0.29 – 1.84	0.51
4	2.47	1.07 – 5.73	0.03
Compliance of radiotherapy	0.18	0.09 – 0.37	<0.0001
Compliance of surgery	0.40	0.40 – 1.08	0.096
Compliance of chemotherapy	0.70	0.41 – 1.21	0.20

Table 6: modelling of recurrent events: AG and WLW

variable	AG			WLW		
	HR	[95% CI]	P	HR	[95% CI]	p
Age at diagnosis	1.01	0.97 - 1.05	0.53	0.89	0.60 - 1.33	0.58
Histology (bone)	1.34	0.95 - 1.91	0.10	1.16	0.62 - 2.15	0.65
2	1.26	0.87 - 1.81	0.22	1.11	0.31 - 3.93	0.87
3	1.58	1.02 - 2.44	0.04	1.36	0.15 - 12.74	0.79
4	1.66	1.02 - 2.71	0.04	2.70	0.11 - 64.25	0.54
Number of relapse	2.04	1.84 - 2.27	<0.001	*	*	*
Compliance of radiotherapy	0.89	0.59 - 1.34	0.58	0.47	0.24 - 0.91	0.03
Compliance of surgery						
Compliance of chemotherapy	1.27	0.88 - 1.82	0.20	1.11	0.63 - 1.96	0.71

*Non included in the model

Table 7: modelling of recurrent events: PWP (time from entry and time from previous event)

variable	PWP (time from entry)			PWP (time from previous event)		
	HR	[95% CI]	p	HR	[95% CI]	p
Age at diagnosis	1.03	0.97 - 1.09	0.31	1.04	0.95 - 1.13	0.39
Histology (bone)	1.39	0.81 - 2.39	0.23	1.56	0.78 - 3.14	0.21
Stage						
2	1.12	0.64 - 1.96	0.70	0.99	0.46 - 2.16	0.99
3	1.55	0.86 - 2.78	0.14	1.24	0.46 - 3.31	0.67
4	1.98	1.12 - 3.50	0.02	2.16	0.92 - 5.06	0.08
Number of relapse	*	*	*	*	*	*
Compliance of radiotherapy	0.70	0.43 - 1.14	0.15	0.40	0.21 - 0.78	0.07
Compliance of surgery						
Compliance of chemotherapy	1.04	0.68 - 1.59	0.87	1.01	0.54 - 1.89	0.98

Table 8: joint frailty analysis

Variable	Coefficient	[95% CI]	p
Risk of relapse			
Age at diagnosis	0.11	0.01 – 0.22	0.03
Metastatic stage	1.29	0.43 – 2.15	0.003
Compliance of radiotherapy	-1.37	-2.28 – -0.47	0.003
Risk of death			
Age at diagnosis	0.11	-0.006 – 0.22	0.06
Histology (bone)	0.86	0.04 – 1.69	0.04
Metastatic stage	1.82	0.6 – 2.77	<0.0001
Compliance of radiotherapy	-1.65	-2.69 – -0.61	0.002
Compliance of surgery	0.57	-0.02 – 1.17	0.06
Compliance of chemotherapy	-0.62	-1.25 – 0.02	0.06

Conflict of interest statement: Nothing to declare.

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