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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.

Marec-Bérard P^{*1}, Aho S^{*2}, Berger C^{3,4}, Plantaz D⁵, Aho-Glelé LS⁶, Ducimetière F², Duclos A⁷, Fontanière B⁸, Collard O⁹, Blay JY², Sunyach MP², Chotel F¹⁰, Bergeron C¹, Dijoud F¹¹, Vaz G¹², Ray-Coquard I².

***P Marec-Bérard & S Aho contributed equally.**

¹ Institut d'Hématologie et d'Oncologie Pédiatrique, Lyon, France

² Centre Léon Bérard & University Claude Bernard Lyon 1, Lyon, France

³ Department of Pediatric Hematology and Oncology Unit, University Hospital of Saint-Etienne & Host Research Team EA4607 SNA-EPIS (Autonomic Nervous System, Epidemiology, Physiology, Exercise, and Health), Jean Monnet University of Saint-Etienne, Saint-Etienne, France

⁴ Childhood Cancer Registry of the Rhône-Alpes Region, University of Saint-Etienne, Saint-Etienne, France

⁵ Department of Pediatric Hematology and Oncology Unit, University Hospital of Grenoble, Grenoble, France

⁶ Department of Epidemiology, University Pediatrics Hospital, Dijon, France

⁷ Centre Lacassagne HCL & Laboratoire Hesper, University Claude Bernard Lyon 1, France

⁸ Centre de Regroupement Informatique et Statistique en Anatomie Pathologique de Rhône-Alpes, Centre Léon Bérard, Lyon, France

⁹ Institut de Cancérologie Lucien Neuwirth, Saint-Priest-en-Jarez, France

¹⁰ Department of Orthopaedic Surgery and Traumatology, Hôpital Femme Mère Enfant, Bron, France

¹¹ Institut multi sites de pathologie, Hôpital Femme Mère Enfant, Bron - University

Claude Bernard Lyon 1, Lyon, France.

¹² Department of Surgery, Centre Leon Berard & Department of Orthopaedic Surgery
and Traumatology, CMCR Massues, Lyon, France

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Corresponding author:

Prof. Isabelle Ray-Coquard, MD, PhD, University of Lyon, Centre Leon Berard,
Department of Medical Oncology, 28 rue Laennec, 69373 Lyon Cedex 08, France. E-
mail: isabelle.ray-coquard@lyon.unicancer.fr ;

Phone +33 (4) 78 78 51 45

Fax +33 (4) 26 55 67 57

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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

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.

INTRODUCTION

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

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

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

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

2 METHODS

2.1 Study population

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

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

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

2.2 Measurement of compliance with clinical practice guidelines

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

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

2.3 Data collection

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

2.4 Statistics

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

2.4.1 Data management, descriptive and bivariate analysis

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

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

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

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

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

2.4.2 Modelling approaches

2.4.2.1 Non recurrent events analysis

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

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

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

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

2.4.2.2 Recurrent events analysis

The first three relapses were taken into account.

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

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

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

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

2.4.2.3 Joint frailty survival analysis

We used a joint frailty model, originally proposed by Liu et al. (23) to jointly model recurrent events and death. Recurrences and survival were modelled in conjunction 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.

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

3.1 Management

The management of all 140 patients was assessed ([Table 2](#)). 30.7% were treated in adult units, 56.4% in paediatric and 12.8% in mixed. 74% of cases were discussed in multidisciplinary tumour board (MTB) in the adult units, 87% in the paediatric units and 100% in the mixed units ($p = 0.026$). The rate of inclusions in clinical trials was 21% in the adult units, 34% in the paediatric units and 56% with joint management ($p = 0.03$). Finally, fertility preservation was achieved in 37% of patients treated in adult sectors versus 59% in paediatric sectors, and 61% in mixed units ($p = 0.046$).

3.2 Compliance with clinical practice guidelines

The analysis of compliance is described in [Table 3](#). Overall compliance with CGPs from initial diagnosis to follow up was only 35%. It was not significantly impacted by the type of care structure since it reached 37% in the adult units, 28% in the paediatric structures and 44% in the mixed ones ($p = 0.415$). Among the compliance of the different sequences of management with CPGs, only the compliance of the initial diagnosis appeared statistically higher in the mixed units (83% vs 53% in adult units and 79% in paediatric structures; $p = 0.007$). The conformity of the other steps of management was not significantly impacted by the type of care structure.

3.3 Overall Survival

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

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

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

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

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

3.4 Relapse free survival

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

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

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

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

3.5 Modelling of recurrent events

3.5.1 Recurrent events analysis

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

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

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

3.5.2 Joint frailty survival analysis

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

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

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

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

4 DISCUSSION

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

5 CONCLUSION

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

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

6 FIGURES

Figure 1: Patient selection

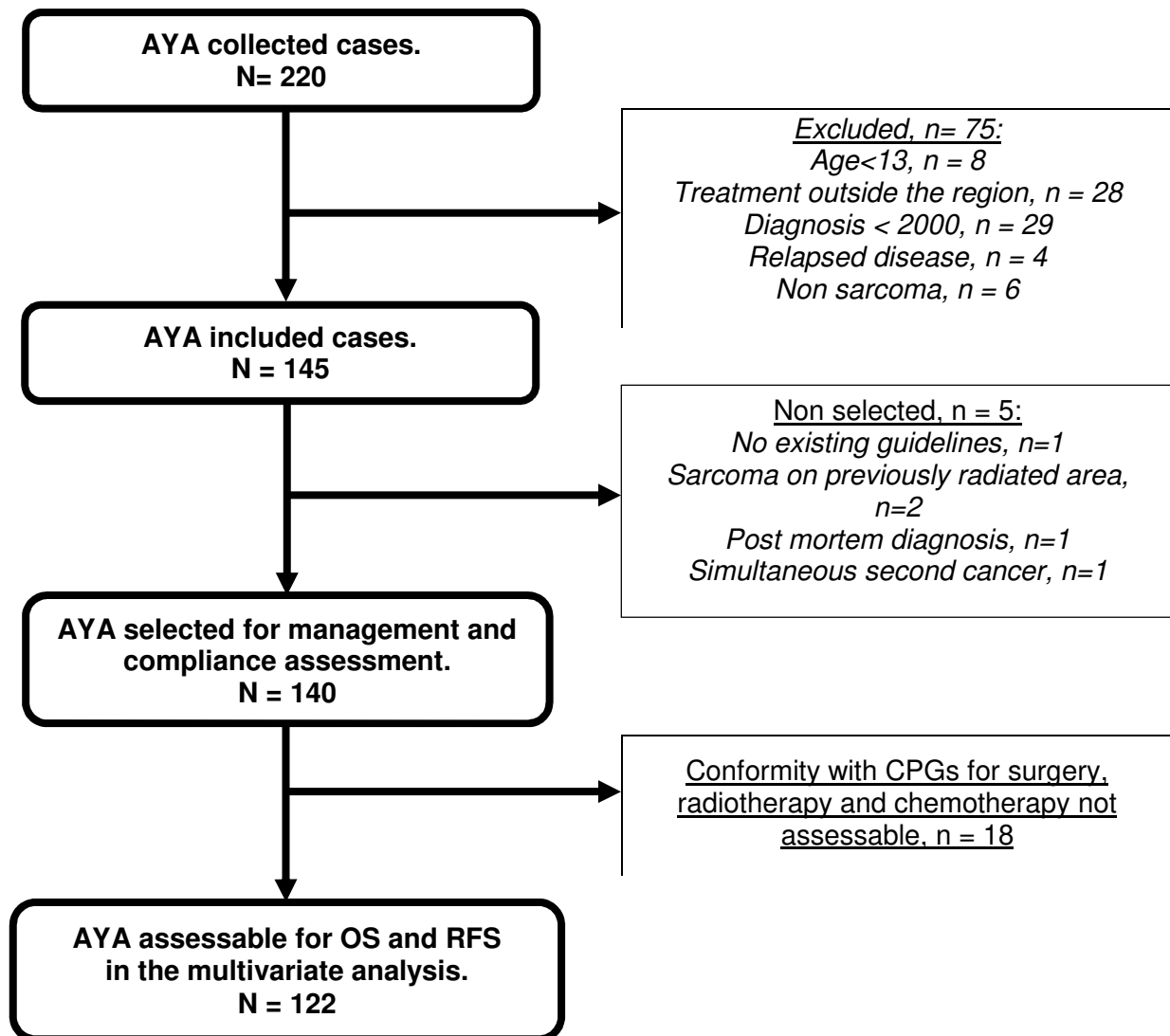
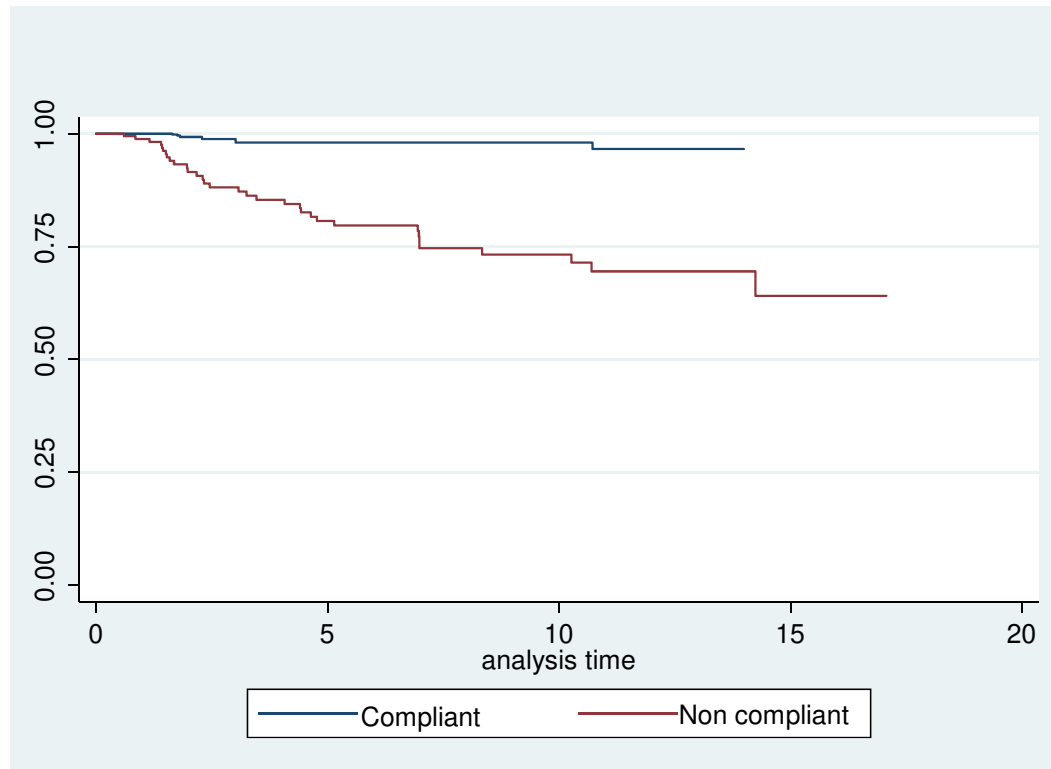


Figure 4: OS according to the compliance of surgery with CPGs, adjusted for age, compliance of radiotherapy with CPGs, histological sub-type and stage



410

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	

412

413

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%)	-	

421 **Table 3: compliance with Guidelines according to sequence of management**
422 **(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%)	-	

423
424

Table 4: multivariate Cox regression model for OS

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

8 ANNEXE SECTION

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

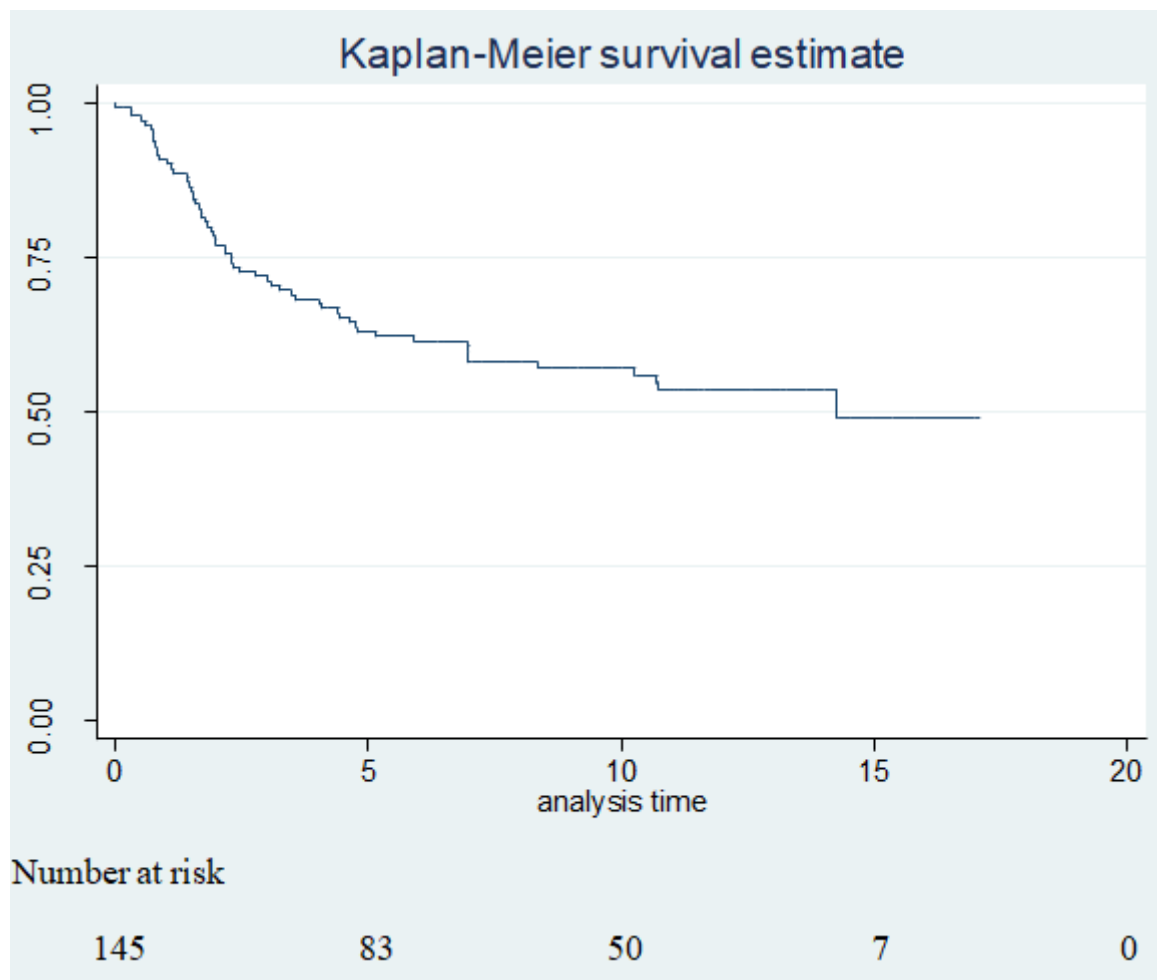


Figure 3: RFS analysis of AYA patients with sarcoma using Kaplan Meier method

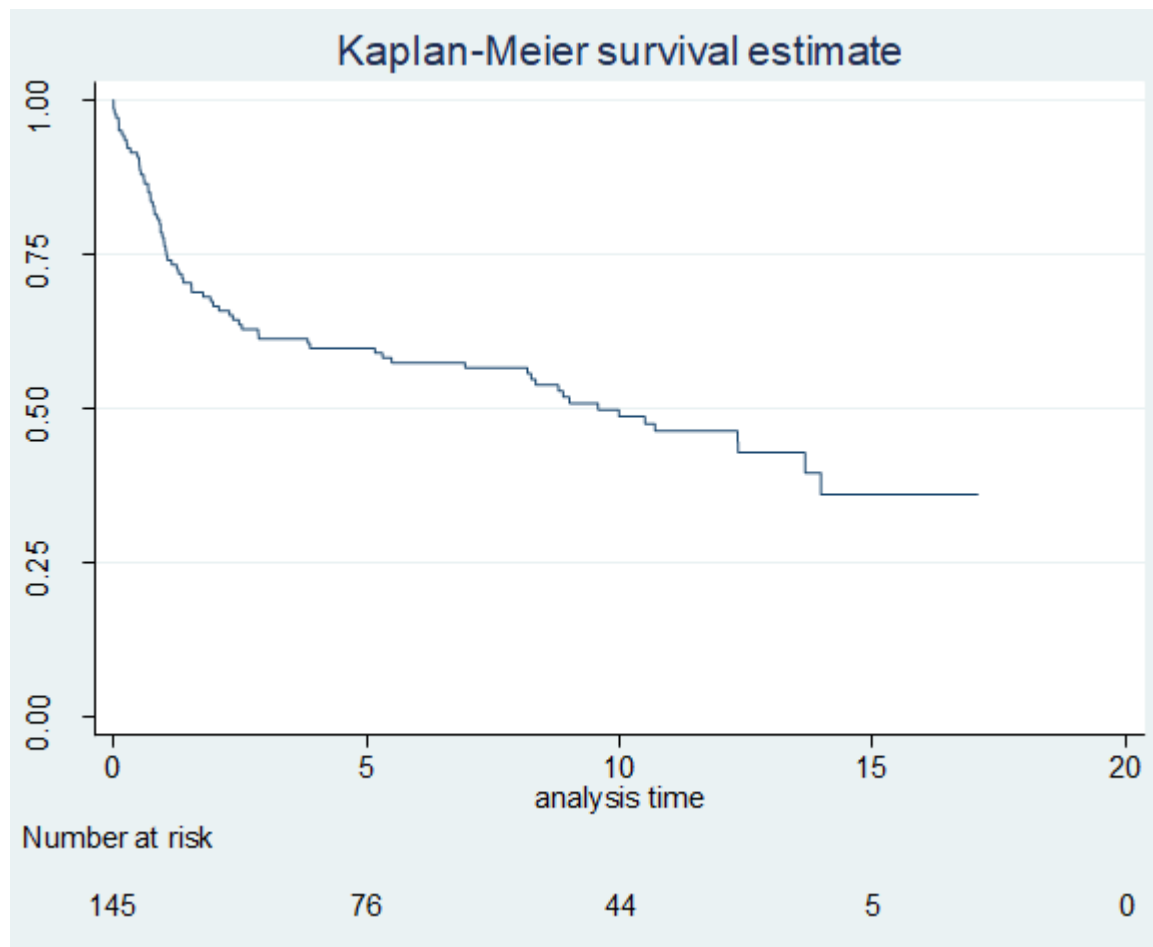


Table 5: multivariate Cox regression model for RFS

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

	AG			WLW		
variable	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)

	PWP (time from entry)			PWP (time from previous event)		
variable	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

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9 REFERENCES

1. Saloustros E, Stark DP, Michailidou K, Mountzios G, Brugieres L, Peccatori FA, et al. The care of adolescents and young adults with cancer: results of the ESMO/SIOPE survey. *ESMO Open*. sept 2017;2(4):e000252.
2. Bleyer A, Choi M, Fuller CD, Thomas CR, Wang SJ. Relative Lack of Conditional Survival Improvement in Young Adults With Cancer. *Semin Oncol*. oct 2009;36(5):460-7.
3. Rainusso N, Wang LL, Yustein JT. The Adolescent and Young Adult with Cancer: State of the Art - Bone Tumors. *Curr Oncol Rep*. août 2013;15(4):296-307.
4. Collins M, Wilhelm M, Conyers R, Herschtal A, Whelan J, Bielack S, et al. Benefits and Adverse Events in Younger Versus Older Patients Receiving Neoadjuvant Chemotherapy for Osteosarcoma: Findings From a Meta-Analysis. *J Clin Oncol*. 20 juin 2013;31(18):2303-12.
5. Selby P, Gillis C, Haward R. Benefits from specialised cancer care. *The Lancet*. août 1996;348(9023):313-8.
6. Friend BD, Tang K, Markovic D, Elashoff D, Moore TB, Schiller GJ. Identifying risk factors associated with worse outcomes in adolescents and young adults undergoing hematopoietic stem cell transplantation. *Pediatr Blood Cancer*. 20 août 2019;e27940.
7. Bleyer A, Montello M, Budd T, Saxman S. National survival trends of young adults with sarcoma: Lack of progress is associated with lack of clinical trial participation. *Cancer*. 1 mai 2005;103(9):1891-7.
8. Desandes E, Lacour B, Sommelet D, Danzon A, Delafosse P, Grosclaude P, et al. Cancer survival among adolescents in France. *Eur J Cancer*. févr 2006;42(3):403-9.
9. Zebrack B, Mathews-Bradshaw B, Siegel S. Quality Cancer Care for Adolescents and Young Adults: A Position Statement. *J Clin Oncol*. 10 nov 2010;28(32):4862-7.
10. Bleyer A. The adolescent and young adult gap in cancer care and outcome. *Curr Probl Pediatr Adolesc Health Care*. mai 2005;35(5):182-217.
11. Bleyer A. ADOLESCENT AND YOUNG ADULT (AYA) ONCOLOGY: The First A. *Pediatr Hematol Oncol*. janv 2007;24(5):325-36.
12. Desandes E, Lacour B, Sommelet D, White-Koning M, Velten M, Tretarre B, et al. Cancer adolescent pathway in France between 1988 and 1997. *Eur J Oncol Nurs*. févr 2007;11(1):74-81.
13. Gatta G, Zigon G, Capocaccia R, Coebergh JW, Desandes E, Kaatsch P, et al. Survival of European children and young adults with cancer diagnosed 1995–2002. *Eur J Cancer*. avr 2009;45(6):992-1005.

14. Desandes E, Lacour B, Belot A, Molinie F, Delafosse P, Tretarre B, et al. Cancer Incidence and Survival in Adolescents and Young Adults in France, 2000–2008. *Pediatr Hematol Oncol.* 11 avr 2013;30(4):291-306.
15. Sommelet D, Pinkerton R, Brunat-Mentigny M, Farsi F, Martel I, Philip T, et al. [Standards, options and recommendations (SOR) for clinical care of rhabdomyosarcoma (RMS) and other soft tissue sarcoma in children. Federation of the French Cancer Centers. French Society of Pediatric Oncology]. *Bull Cancer (Paris).* déc 1998;85(12):1015-42.
16. [Standards, options and recommendations (SOR) for diagnosis, treatment and follow-up of osteosarcoma. Available on <https://www.ncbi.nlm.nih.gov/pubmed/10066947>
17. The ESMO/European Sarcoma Network Working Group. Bone sarcomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol.* 1 sept 2014;25(suppl 3):iii113-23.
18. Territorial inequalities in management and conformity to clinical guidelines for sarcoma patients: an exhaustive population-based cohort analysis Available on <https://www.ncbi.nlm.nih.gov/pubmed/23933822>
19. Ray-Coquard I. Conformity to clinical practice guidelines, multidisciplinary management and outcome of treatment for soft tissue sarcomas. *Ann Oncol.* 1 févr 2004;15(2):307-15.
20. Trends in treatment-related deaths (TRDs) in childhood cancer and leukemia over time: a follow-up of patients included in the childhood cancer registry Available on <https://www.ncbi.nlm.nih.gov/pubmed/18300318>
21. Royston P, Ambler G, Sauerbrei W. The use of fractional polynomials to model continuous risk variables in epidemiology. *Int J Epidemiol.* oct 1999;28(5):964-74.
22. Cook RJ, Lawless J. *The Statistical Analysis of Recurrent Events* [Internet]. New York: Springer-Verlag; 2007 (Statistics for Biology and Health).
23. Liu L, Wolfe RA, Huang X. Shared frailty models for recurrent events and a terminal event. *Biometrics.* sept 2004;60(3):747-56.
24. Desandes E, Bonnay S, Berger C, Brugieres L, Demeocq F, Laurence V, et al. Pathways of care for adolescent patients with cancer in France from 2006 to 2007. *Pediatr Blood Cancer.* juin 2012;58(6):924-9.
25. Albritton K, Bleyer WA. The management of cancer in the older adolescent. *Eur J Cancer.* déc 2003;39(18):2584-99.
26. Shochat SJ, Fremgen AM, Murphy SB, Hutchison C, Donaldson SS, Haase GM, et al. Childhood Cancer: Patterns of Protocol Participation in a National Survey. *CA Cancer J Clin.* 1 mars 2001;51(2):119-30.
27. Birchall MA, Bailey D, Lennon A. Performance and standards for the process of head and neck cancer care: South and West audit of head and neck cancer 1996–1997 (SWAHN I). *Br J Cancer.* août 2000;83(4):421-5.

28. Tan AL, Jones R, Mcpherson G, Rowan D. Audit of a multidisciplinary vulvar clinic in a gynecologic hospital. *J Reprod Med.* août 2000;45(8):655-8.
29. Wöckel A, Kurzeder C, Geyer V, Novasphenny I, Wolters R, Wischnewsky M, et al. Effects of guideline adherence in primary breast cancer—A 5-year multi-center cohort study of 3976 patients. *The Breast.* avr 2010;19(2):120-7.
30. Blay J-Y, Honoré C, Stoeckle E, Meeus P, Jafari M, Gouin F, et al. Surgery in reference centers improves survival of sarcoma patients: a nationwide study. *Ann Oncol.* 1 juill 2019;30(7):1143-53.