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Extracranial rhabdoid tumours: results of a French series of patients treated with a dose compression strategy according to EpSSG recommendations

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ABSTRACT

Background and aims: Extracranial malignant rhabdoid tumours (MRTs) are tumours that mainly affect young children and have a poor prognosis. In 2014, the European Pediatric Soft-tissue Sarcoma Group (EpSSG) developed treatment recommendations consisting in intensive dose chemotherapy every two weeks using VDCy (vincristine-doxorubicin-cyclophosphamide) and IE (ifosfamide-etoposide) associated with early surgery and irradiation of tumour sites.

Methods: A retrospective study was conducted on children treated in France by these new recommendations up to January 2019.

Results: Thirty-five patients were identified. The primary tumour was in miscellaneous soft parts for 18 patients, in the kidney for 11 and in the liver for six. The median age at diagnosis was 17.5 months (range 1.2 – 198.2). Distant locations (metastatic or synchronous tumours) were present in 37.1% at diagnosis. *SMARCB1* germline pathogenic variant was detected in 17.1% of patients. Overall tolerance was good, with 87% to 97% of theoretical chemotherapy cumulative doses actually delivered. The median interval between two courses was 18 days. Surgical resection was performed in 83% (19 R0, 7 R1, 3 R2) and local radiotherapy in 49% of patients. After a median follow-up of 50.4 months (range 16.5 – 134.1), the 2-year overall (OS) and event free survivals (EFS) were 47.6% (95% CI 30.2 – 63.1) and 42.9% (95% CI 26.5 – 58.3) respectively. On univariate analyses, localized disease and gross total resection were significantly associated with favorable outcomes.

Conclusions: Intensive dose chemotherapy with VDCy/IE can be administrated with no remarkable short-term toxicity, including in infants. However, the outcome remains poor for patients without gross total resection and with metastatic or multifocal disease. These patients could be stratified into a high-risk group that requires a new immediate therapeutic approach such as targeted agents combined with multimodal therapy.

Abstract word count: 282

INTRODUCTION

Extracranial malignant rhabdoid tumours (MRTs) are rare aggressive tumours characterized by the so-called “rhabdoid phenotype” within largely undifferentiated cell [1,2]. The most frequent anatomic locations of MRT are soft tissues, kidneys (so-called “RTK”) and finally MRT of the liver [3]. The incidence in the United Kingdom has been estimated to be 4 per million for children under 12 months of age compared to 0.6 per million for children over 1 year of age, with no difference between males and females [4]. MRT generally occur before 3 years of age and about 30% are metastatic at diagnosis [5–8].

MRTs are characterized by the almost constant biallelic inactivation of the tumour suppressors gene *SMARCB1*, more rarely *SMARCA4*, on chromosome 22q11.2 and 19p13.2, respectively [9,10]. *SMARCB1* encodes the BAF47 protein (also called INI1/SNF5) which is part of the SWI/SNF (switch mutants/sucrose non-fermenting, also named “BAF”) chromatin remodeling complex [11]. A heterozygous germline pathogenic variant in *SMARCB1* gene (or *SMARCA4*) has been reported in about 25% of children with MRTs at any age and up to 60% in children under 6 months of age [12–14], especially those with multifocal or combined CNS and extra-cranial rhabdoid tumours [15].

Despite multimodal and aggressive therapeutic approaches, the prognosis of MRTs remains poor with a 2 to 5-year overall survival (OS) between 18.4% and 38.6% in historical cohorts, all stages combined, using heterogeneous types of chemotherapy [5–8,16,17]. Thus, and due to the low incidence of MRTs, there is no international therapeutic standard at present time. Early surgical treatment is deemed to be important given the transient chemosensitivity of MRTs, in order to maximize the chance to obtain a complete response which might be of prognostic value [16,18]. Radiotherapy is also suggested to be associated with a favorable outcome, but confounding factors such as older age and controlled disease upon chemotherapy limit the assessment of its actual prognostic value [3,7,14,16].

The European Paediatric Soft Tissue Sarcoma Group (EpSSG) has published in 2016 the results of a multinational prospective study (2005-2014) based on an intensive multimodal therapy: Vincristine, Doxorubicin, Cyclophosphamide (VDCy) and Cyclophosphamide, Carboplatin, Etoposide (CyCE) every 3 weeks, surgical treatment as soon as possible and irradiation of all affected sites. The 3-year event free survival (EFS) and OS were 32.3% and 38.4% respectively; patients whose tumour progressed during treatment or with metastatic disease harbored an even worse outcome with a 2-year OS of 13.0% [16]. Improving the treatment efficacy with a different backbone of conventional chemotherapies is therefore highly warranted.

In 2012, Womer et al published an interval-compressed chemotherapy backbone alternating Vincristine, Doxorubicin, Cyclophosphamide (VDCy) and Ifosfamide, Etoposide (IE) every two weeks applied to patients with localized Ewing sarcomas. They could demonstrate a highly tolerable toxicity of such a dose-intense treatment scheme [19]. Waldron et al reported the benefit of this treatment in a 31-month-old boy with stage IV RTK [20]. Inspired by these experiences and aiming to increase the dose intensity, the EpSSG proposed the VDCy/IE alternance backbone as treatment guidelines for children with MRT since 2014. Here, we report the French experience on patients with MRT treated since 2014, focusing on the results of the EpSSG recommended treatment.

MATERIAL AND METHODS

Patients and Study Design

A retrospective study was conducted using medical records of patients treated in France for a MRT between January 2014 and December 2018 and before 2014 if they had been treated by VDCy/IE. In order to identify the patients, we investigated the database from the Unité de Génétique Somatique (Institut Curie, Paris, France) which is the national reference laboratory for *SMARCB1* mutations of MRTs and interviewed 29 French pediatric cancer centers. Patients were included when they were aged 0 to 18 years on the treatment start date and treated in France for a primary MRT, including kidney, liver and miscellaneous soft parts. The diagnosis was defined by compatible histological features associated with a negative staining with INI1 or BRG1 antibodies and/or with a biallelic inactivation of one of these two genes assessed by molecular biology. Untreated patients, patients treated for an ATRT (Atypical Teratoid Rhabdoid Tumour), in the central nervous system, or according to ATRT-specific protocol, and patients with neither histological nor molecular documentation of the *SMARCB1/SMARCA4* deficiency were excluded.

Chemotherapy interval compressed strategy according to EpSSG recommendations

The recommendations were applied regardless of the tumour anatomical location, and whatever the metastatic status at diagnosis. The recommended chemotherapy, after initial surgery or biopsy, was given for 28 weeks and radiotherapy was recommended for all tumour sites ([Appendices for details of the recommendations](#)). High-dose chemotherapy (HDCT) and maintenance therapy were not specifically recommended. Information on patients treated according to other protocols or treatment recommendations were collected.

Toxicity

Toxicities were assessed according to the CTCAE v.5 (common terminology criteria for adverse events). Toxicities > grade 2 of the different local and systemic treatments were reported.

Statistical analyses

The data were collected via a computerized case report form (CRF) and analyzed at the Curie Institute, with a data cut-off on 30/05/2020. All data analyses were performed using PRISM software (v.9). Survival time was calculated from the date of diagnosis to the date of the event (progression, relapse, second cancer or death) or last follow-up point, using the Kaplan-Meier method. To evaluate the actual tumour response rate to VDCy/IE, and given the few initial misdiagnoses leading to inappropriate first-intent treatment, the EFS was calculated from the diagnosis to the first event reported after the initiation of VDCy/IE treatment. Patients alive at the end of the study were censored

at the date of the last follow-up point. The heterogeneity of survival among the strata of selected variables was compared by the log-rank test. Survival between two high risk (HR) and standard risk (SR) stratify patients' groups was compared as recently proposed by Nemes et al. [14]. Statistical significance was defined by a $p < 0.05$. Nonparametric testing was performed using the Fisher's exact test for qualitative variable and the Mann-Whitney and Kruskal-Wallis tests for quantitative variable.

Regulatory Approvals

This study was approved by the Institutional Review Committee (CRI data) of the Institut Curie (Paris, France). This study was declared compliant with the reference methodology MR-004 of the French National Commission for Information Technology and Liberties (CNIL). In accordance with the general regulation on data protection (RGPD), the legal representatives of living patients were informed by letter of the completion of this study.

RESULTS

Patients of the study

Sixty French patients were diagnosed with extracranial MRT, four before 2014 (treated by the EpSSG recommended treatment) and 56 between 2014 and 2018. Altogether, 50 patients fulfilled inclusion criteria of the study. Thirty-five patients were treated by VDCy/IE according to EpSSG recommendations: 26 patients (74.3%) straightforward and 9 patients (25.7%) after 1 or 2 courses of another treatment because of i) initial misdiagnosis (nephroblastoma in four patients, embryonic rhabdomyosarcoma in two and hepatoblastoma in one), ii) an emergency treatment for a spinal cord compression, or iii) tailored treatment for young age (Figure 1). Fifteen patients were treated otherwise (Details in supplemental Table I).

Characteristics of patients treated with VDCy/IE at diagnosis

No significant difference was found regarding clinical and biological characteristics at diagnosis between patients treated with VDCy/IE or otherwise in the same period (Table I). Relying on this absence of bias, further analyses focus only on the 35 patients treated by the VDCy/IE regimen throughout the manuscript.

The median age at diagnosis was 17.5 months (range 1.2 – 198.2) with 14 patients (40%) younger than 1 year (Table I). Of note, three patients were older than 10 years. The primary tumour was located in extrarenal soft tissues in 18 patients (51.4%), in the kidney in 11 (31.4%) and in the liver in six (17.1%). The age distribution and the extension according to the site of the primary tumour are shown in Figure 2. Distant tumour locations were observed in 13 patients (37.1%); since molecular analyses of distant locations were not available, metastatic and synchronous multifocal diseases could not be formally distinguished. Among 4 patients who had distant CNS location, 3 carried a germline mutation (patients n°12, 30, 33); for the last one without evidenced germline mutation (n°31), the tumour location was paraspinal and CNS location refers to the leptomeningeal metastatic spread.

SMARCB1 somatic pathogenic variant was identified in the tumour of 29 patients (82.9%); one patient had no screening and five patients non-informative specimen, all with negative BAF47 immunohistochemical staining. None of the tumour demonstrated a loss of *SMARCA4* within patients treated according to EpSSG guidelines. Heterozygous *SMARCB1* germline alteration was identified in six out of 33 tested patients (18.2%). For five patients, we cannot rule out a germline mutation since no tumour mutation was identified (Details in supplemental Table II).

Compressed chemotherapy interval strategy does not increase toxicity, including infants

Full chemotherapy treatment as per EpSSG guidelines (maximum 14 courses) was administered to 14 patients (40%) within median treatment duration of 8.1 months (6.8 – 10.7, theoretical duration 6.5 months). The median number of chemotherapy courses really administered was 9 (1 – 14), as compared with 14 theoretically planned, due to disease progression and not toxicity. Among the 21 patients who received a shortened chemotherapy treatment, 14 (66.7%) discontinued the treatment for early progression and four (19%) because they received HDCT (after 8 to 11 courses); other reasons for early discontinuation were irradiation-related death (n=1), excessive toxicity (n=1), and medical decision (n=1). The mean rate of chemotherapy dose received compared to that recommended was 97.4% for vincristine, 90.5% for doxorubicin, 96.3% for cyclophosphamide, 87.6% for ifosfamide and 87.4% for etoposide (Figure 4A) without variation according to the age of the patients (Supplemental Figure 1). The median interval between courses n°1 and n°4 was 47.5 days with no difference between age subgroups (Figure 4B). The median interval between two courses was 18 days (16.5 days in <12 months, p=0,8) (Figure 4C).

The most common toxicities were bone marrow suppression, febrile neutropenia and mucositis. Three patients had notable adverse events related to conventional chemotherapy. One presented a septic shock secondary to bacteriemia, one a grade 3 cardiac dysfunction, one a grade 3 hematuric cystitis. No permanent toxicity or toxic death related to chemotherapy was noted.

Local treatment

Surgical resection of the primary tumour was performed in 29 patients (82.9%): two up-front complete resections (R0) of RTK (1 with M0 and 1 with M+ disease) and 27 delayed resections after chemotherapy (18 with M0 and 9 with M+ diseases), after a median of 4 courses (Table II). The median time between diagnosis and surgical resection was 82 days (0 – 166), with earlier resection in case of RTK (Figure 4). For two patients with localized tumours, R0 resection was achieved with a radical mutilating surgery (right radiocarpal amputation and right upper limb disarticulation) in order to maximize the survival chance. Noteworthy, four patients who had a near complete resection (R1, patients n°2, 8, 11, 16) and one with an incomplete resection followed by radiotherapy (R2, patient n°4) were alive with no evidence of disease at the last follow-up.

Irradiation of the primary tumour site was performed in 17 patients (48.6%), either after surgical resection of the primary tumor (n=15) or without (n=2) (Table II). The majority of RTK (8/11) was irradiated, unlike soft parts MRTs (8/18) and hepatic MRT (1/6). Age below 12 months was associated with lack of irradiation of the primary tumour site with an odds ratio of 7.3 (95% CI 1.46 – 29.0; p = 0.015) (Figure 4). A bi-pulmonary irradiation at 15 Gy in 10 fractions was delivered for metastasis of RTK in 2 patients, one of whom (8.6 months at diagnosis, patient n°28) died secondary to respiratory failure 71 days after the irradiation.

The others > grade 2 toxicities related to radiotherapy were: esophagitis (n=1), mucositis (n=1) for irradiation of para-spinal tumours, veno-occlusive disease (n=1) for a liver tumour, and long terms thoracic deformity (n=1, scoliosis after treatment of a tumour invading the ribs).

Survival outcomes

Details of the outcome of patients treated with a chemotherapy interval compressed strategy according to the EpSSG recommendations are presented on the [Figure 5](#). At the end of follow-up, 17 patients (48.6%) were alive (15 with M0 and 2 with M+ diseases), 16 patients without disease and 1 patient with progressive disease of a tumour deemed to be a second primary MRT in a predisposition context. As shown on [Figure 5](#), none of the CR was achieved by chemotherapy only. Eighteen patients (51.4%) died, 17 secondary to progression of their disease and 1 due to radiotherapy-related toxicity. Median follow-up for alive patients was 50.4 months (range 16.5 – 134.1). The 2-year OS and EFS were 47.6% (95% CI 30.2 – 63.1) and 42.9% (95% CI 26.5 – 58.3), respectively ([Figure 6A](#)). Median time to progression was 3.6 months (1 – 12.5). On univariate analysis, only distant locations (M+) and lack of gross total resection (GTR) were significantly associated with poor survival ([Figure 6B, C&D](#)). The presence of a germline mutation increased the risk of distant locations at diagnosis ($p = 0.00083$). Using Nemes et al. stratification, the 2-year OS of patients treated by VDCy/IE was significantly higher for the SR than the HR group (72.2% vs 22,1%, $p = 0.0006$) ([Figure 6E](#)). Age below 12 months at diagnosis, presence of a germline pathogenic variant and lack of local radiotherapy appeared to be unfavorable prognostic factors but were not statistically significant ([Figure 6F](#)). The estimated 2-year OS according to clinical and therapeutic characteristics is listed in [supplemental table III](#).

DISCUSSION

Our results show that dose-intensity chemotherapy alternating VDCy and IE every 2 weeks, can be safely administered to pediatric patients including infants. The full length of treatment could be administered to 40% of patients, which is comparable to the previous EpSSG cohort experience [16], with a high ratio of delivered/expected dose intensity. The median time between two courses was 18 days slightly more than the theoretical 14 days, but this mean value is partly biased by surgery or radiotherapy-related delays. Altogether, the tolerance is completely acceptable, even in the youngest patients.

The 47.6% and 42.9% 2-year OS and EFS, respectively, have to be compared to previously published cohorts. Four patients experienced early progression upon adjuvant therapy: three were misdiagnosed RTs and was a neonatal case receiving, respectively, unappropriated chemotherapy and low-toxicity combination. However, the EFS was calculated from the date of the start of relevant treatment, to avoid an overestimation of the rate of chemoresistance. Historical series have reported OS between 18.4% and 38.6% [5–8]. In the previous EpSSG cohort treated with VDCy/CyCE, the 3-year OS was 38.4%, although the rate of metastatic tumours was lower (23% vs 37.1%); in addition, the cumulative dose of cyclophosphamide was much higher in the previous EpSGG guidelines (17.0 g/m² vs 8.4 g/m²) ([Supplemental Table IV](#)) [16]. In the EU-RHAB registry, the 45.8% 5-year OS and the 35.2% 5-year EFS are comparable with our results, with a similar rate of metastatic cases (35% vs 37.1%); results remain similar whatever the metastatic status or the extension of resection. The main difference between the EU-RHAB and VDCy/IE schedules are the higher chemotherapy cumulative doses in the former; however, we noticed a remarkably good tolerance of VDCy/IE even in the younger, with no recurrent concerning side-effects [14]. Hence, assuming the very low incidence of tumour events after two years in our series, the dose-intense strategy appears at least equivalent to the EU-RHAB recommendations and the previous EpSSG results.

Our series confirmed the importance of local treatment, as gross total surgical resection was associated with improved survival (2-year OS of 57.7%), as recently reported [5,14]. Nevertheless, 4 patients (patients n°18, 21, 23 and 24; GLM ruled out) of this cohort experienced relapse after CR (reached with an R0 resection) of an initially localised disease (M0). This strongly suggests that a systemic treatment is needed even in the absence of persistent local disease because of the intrinsic dissemination capacity of RTs. The impact of local irradiation on tumour control has been suggested elsewhere [3,5], but it did not reach significance in our cohort. Seeringer and colleagues suggested that even infants may benefit from radiation therapy on the tumour site, assuming a tolerable risk; however, our series illustrates that the expected acute and long-term radiation-related toxicity is still limiting the rate of tumour site irradiation in children below 12 months and decision regarding

radiotherapy should result from treating physician and parents [21]. Especially for patients with M0 disease and GTR, the benefit of radiotherapy is still not proven. Indeed, we observed a long survival in 6 patients with M0 disease and without radiotherapy: 2 patients with R1 resection (patients n°2 and 8) and 4 patients with R0 resection (patients n°9, 10, 15, 17). This could be put in link with the German group results [22]. Concerning distant metastasis, Melchior et al. demonstrated that the lack of radiotherapy (with dosage: 15–30 Gy) to all involved tumour sites in patients with RTK is associated with a decreased survival (2-year PFS 15.4% vs 66.7%; $p < 0.001$). They also reported a statistically significant survival improvement in the 2-year PFS for patients with irradiated lung and/or mediastinal metastases (60 % vs 6%; $p = 0.006$) [22]. However, the toxicity of such irradiation in infants has to be taken into account, as exemplified by the toxic death in one patient of our cohort.

SMARCB1 germline pathogenic variant was found in 18.2% of the patients, which is in accordance with a previous prospective study and lower than retrospective series [12–14]. Presence of a germline mutation was not found to confer a poorer prognosis in terms of OS but was associated with an increased risk of distant locations at diagnosis ($p = 0.00083$); consistently, the 1 year of age cut-off was not either found to be prognostic, in contrast with previous historical series, but this may be due to the limited cohort size [7,8,14,16]. Distant tumour locations confer a very poor prognosis (2-year OS of 15.4%), as previously reported [14,16]; remarkably, two patients with M+ disease were still alive after the end of follow-up (patients n°3 and n°12).

Maintenance therapy had never been evaluated for MRTs but was still administered in seven patients in our cohort. All are in sustained remission; noticeably, one had distant tumour locations at diagnosis. Among the five patients (three M0 and two M+ disease) of our series who received HDCT, only one patient with M+ disease died, reviving the controversy on the potential value of performing HDCT for metastatic chemosensitive tumours [6,23,24]. One should however keep in mind that all these patients had achieved CR previously to HDCT, which may obviously introduce a selection bias.

Using the same risk model of stratification than Nemes et al. in our cohort, patients with HR disease (M+ disease and/or lack of GTR and/or germline pathogenic variant) had a worse 2-year OS (22.1%, vs 72.2%) [14]. For these patients, treatment could be improved by adding targeted therapies, avoiding cumulative hematological toxicity, such as epidrugs in development (e.g. EZH2 or HDAC inhibitors) [25,26]. Checkpoint inhibitor could also be considered in some cases, given the immune infiltrate and immunogenicity of MRTs recently reported [27], and some tumour responses observed upon anti-PDL1 (atezolizumab) [28,29] and anti-PD1 treatment (pembrolizumab) [30]. Recently, Chun et al. described five DNA methylation subgroups in rhabdoid tumours (RTs); three of them shared T cell patterns consistent with a potential role for immunotherapy [31,32]. Further subgroups

characterizations might improve the understanding of RTs biology and ultimately reveal some new potential targets or more tailored treatments.

As a retrospective study of national practices based on recommendations, and not as an actual prospective phase II trial, our work leads to limited conclusions regarding the actual benefit of this particular regimen, irradiation or maintenance chemotherapy. Altogether, multimodal therapy including intensive interval-reduced chemotherapy, surgical resection, and radiotherapy, whenever feasible, brings among the best survival results reported so far. However, the most appropriate burden of treatment still needs to be evaluated especially for M0R0 diseases and the outcomes remain far below our expectancies. The next trials may aim at combining targeted therapies with this backbone, the good tolerance of which may safely allow such innovative approaches.

CONFLICT OF INTEREST STATEMENT

We hereby confirm that there are no conflict of interest disclosures from any authors and there was no funding statement for this study.

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Tables and figures

Table I. Clinical and biological characteristics of patients according to the treatment

	VDCy/IE N = 35 (70%)	Other treatments N = 15 (30%)	Total N = 50	
	N	N	N	%
Age (months) at diagnosis				
Median (min – max)	17.5 (1.2 - 198.2)	18.7 (1.2 - 120.0)	17.7 (1.2 – 198.2)	
< 12	14	5	19	38
12 – 36	12	4	16	32
> 36	9	6	15	30
Gender				
Female	15	8	23	46
Male	20	7	27	54
Sex ratio (M/F)	1.33	0.88	1.17	
Tumour molecular diagnosis				
Undone	1	0	1	2
<i>SMARCB1</i> mutation	29	12	41	82
<i>SMARCA4</i> mutation	0	1	1	2
No mutation identified	5	2	7	14
Germline mutation				
No	27	8	35	70
Yes	6	4	10	20
Undone	2	3	5	10
Site of origin of primary tumour				
Kidney	11	7	18	36
Liver	6	1	7	14
Soft parts	18	7	25	50
Tumour size				
A: ≤ 5 cm	9	1	10	20
B: > 5 cm	26	14	40	80
Distant locations				
M0, LN-	13	10	23	46
M0, LN+	9	0	9	18
M+	13	5	18	36
Site of distant locations¹				
Lung only	9	2	11	
CNS only	1	-	1	
Left adrenal gland	-	1	1	
Lung and hepatic	-	1	1	
Lung and CNS	1	1	2	
Visceral and CNS	1	0	1	
Lung, CNS, pelvic & muscular	1	0	1	

CNS: central nervous system; Cy: cyclophosphamide; D: doxorubicin; E: etoposide; I: ifosfamide; M0, LN-: localized disease without loco-regional lymph node involvement; M0, LN+: localized disease with loco-regional lymph node involvement; M+: distant tumour locations; V: vincristine.

Table II. Local treatment of patients treated by VDCy/IE (n=35)

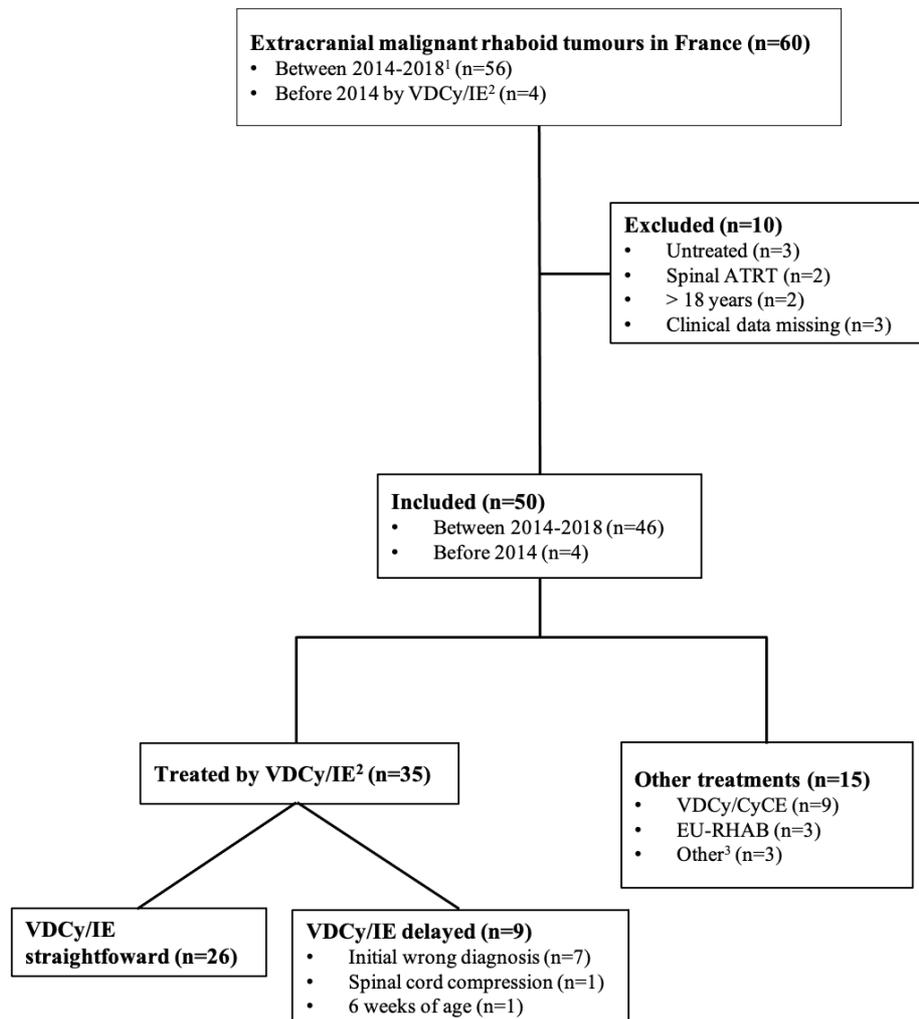
	M0	M1	Total		M0	M1	Total
Radiotherapy	12	5	17	Surgery	19	10	29
Photons	9	3	12	Kidney	4	7	11/11
Protons	3	2	5	Liver	3	1	4/6
				Soft parts	12	2	14/18
No radiotherapy (reasons)	10	8	18	No surgery (reasons)	3	3	6
Progressive disease	2	7	9	Progressive disease	2	3	5
Young age ^a and R0	4	1	5	Unresectable paraspinal tumour	1	-	1
Older patients ^b	2	-	2				
Young age ^a despite R+	1	-	1				
Parental refusal	1	-	1				

^a Median 4,4 months (range 1,7-7,1)

^b Patients with too large volume and/or expected too high toxicity (13.7 and 96 months)

M0: localised disease; M1: metastatic disease; R0: complete resection; R+: incomplete tumoral resection (R1 or R2)

Figure 1 - Flow chart of the study



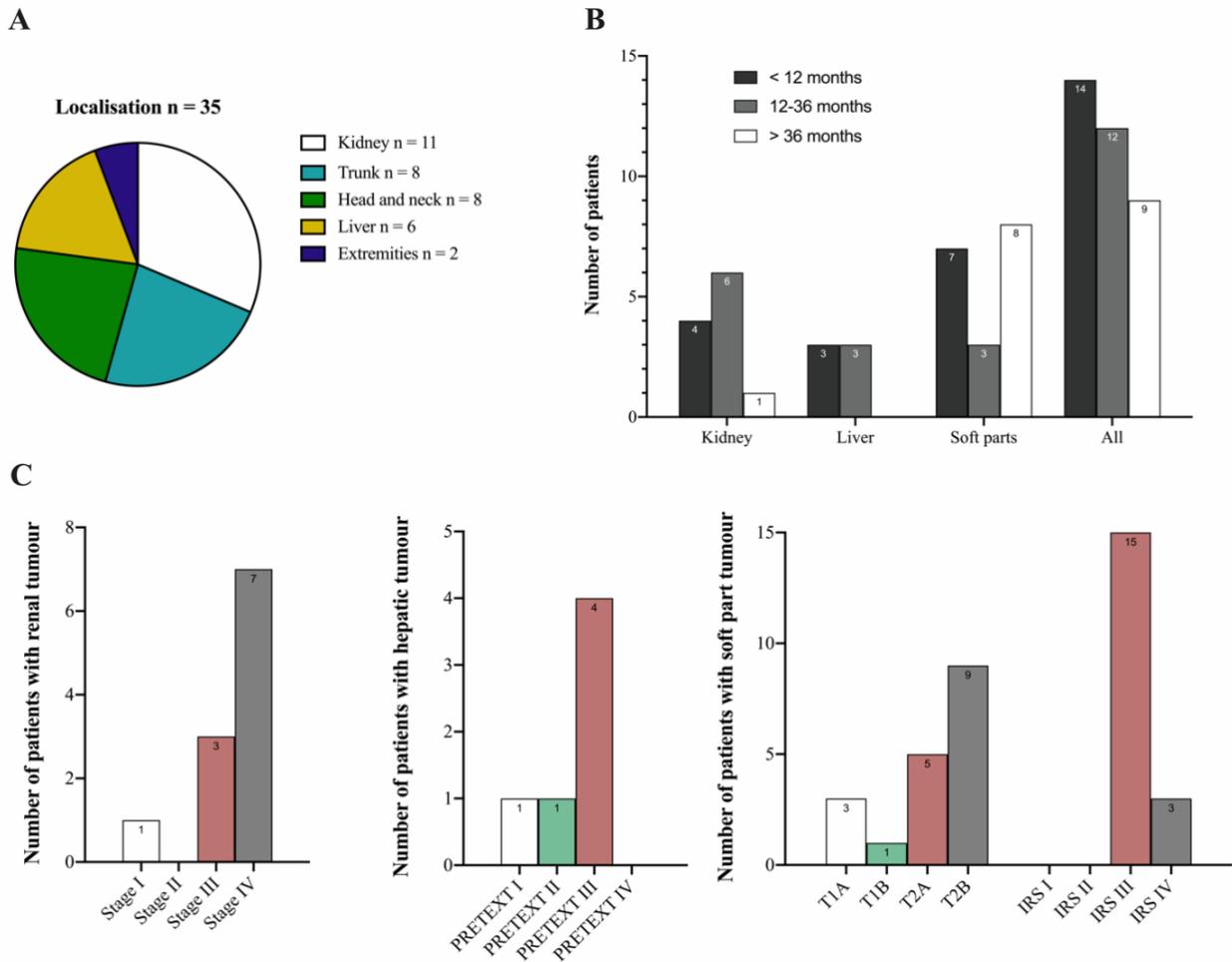
¹ Whatever the treatment regimen.

² According to EpSSG NRSTS version 1.2 (January 2014).

³ Personalized treatment plans.

ATRTR: atypical teratoid rhabdoid tumour; CyCE: cyclophosphamide, carboplatin, etoposide; EpSSG: European paediatric soft tissue sarcoma study group; EU-RHAB: European rhabdoid registry; IE: ifosfamide, etoposide; NRSTS: non-rhabdomyosarcoma soft tissue sarcomas; VDCy: vincristine, doxorubicin, cyclophosphamide.

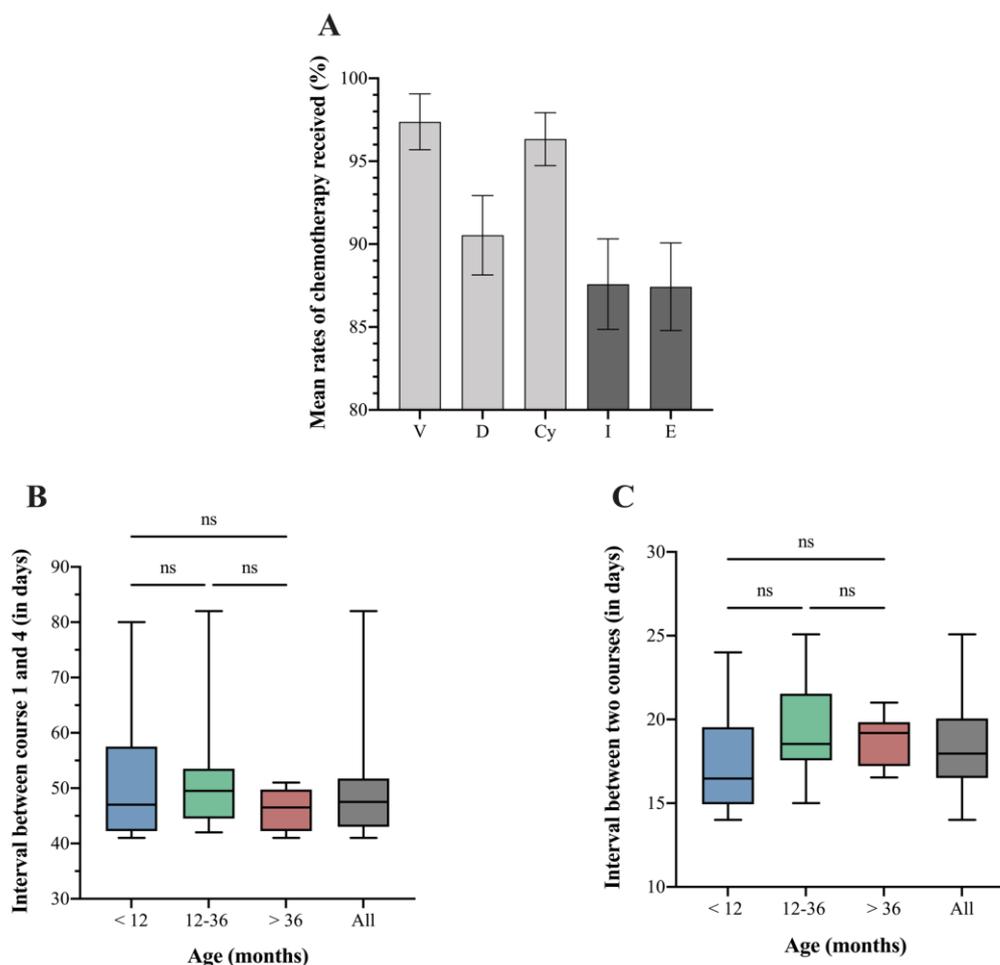
Figure 2 - Characteristics of the primary tumour treated by VDCy/IE (n=35)



A. Repartition of site origin of primary tumour. **B.** Age distribution according to site origin of primary tumour. **C.** Staging of renal tumours according to the SIOP classification, liver tumours according to the PRETEXT classification and soft parts tumours according to the pre-treatment TNM classification before surgery and IRS after surgery.

IRS: intergroup rhabdomyosarcoma study; PRETEXT: pre-treatment extent of tumour; SIOP: international society of paediatric oncology; Soft parts: trunk, head and neck and extremities.

Figure 3 - Toxicity of dose intensity treatment with VDCy alternating with IE (n=35)

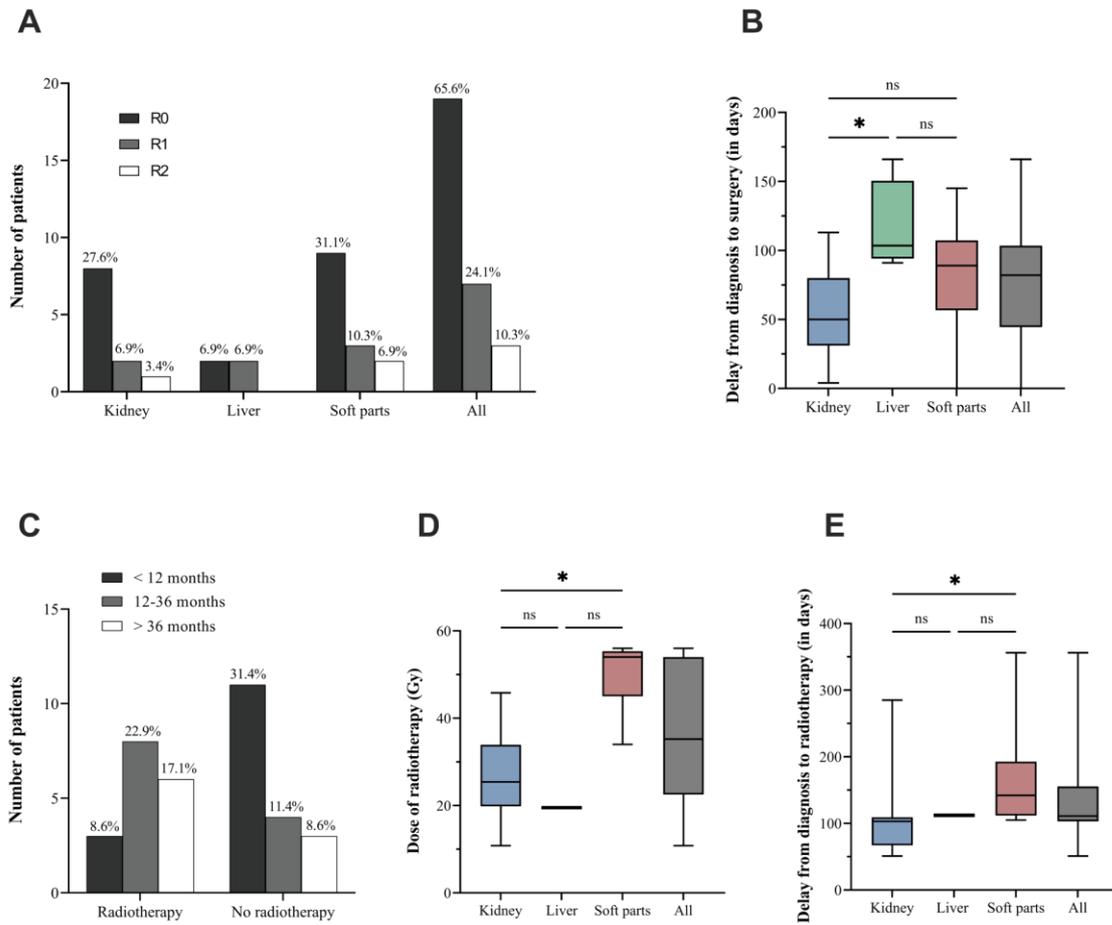


A. Mean (with SEM) rates of chemotherapy of the cumulative doses actually administered and the theoretical cumulative dose planned per protocol for each drug. **B.** Median interval in days between course 1 (first VDCy) and course 4 (second IE) with a theoretical interval of 42 days. **C.** Median interval between two courses (VDCy and IE or IE and VDCy) with a theoretical interval of 14 days.

Age representation: < 12 months (n=14), 12-36 months (n=12), > 36 months (n=9).

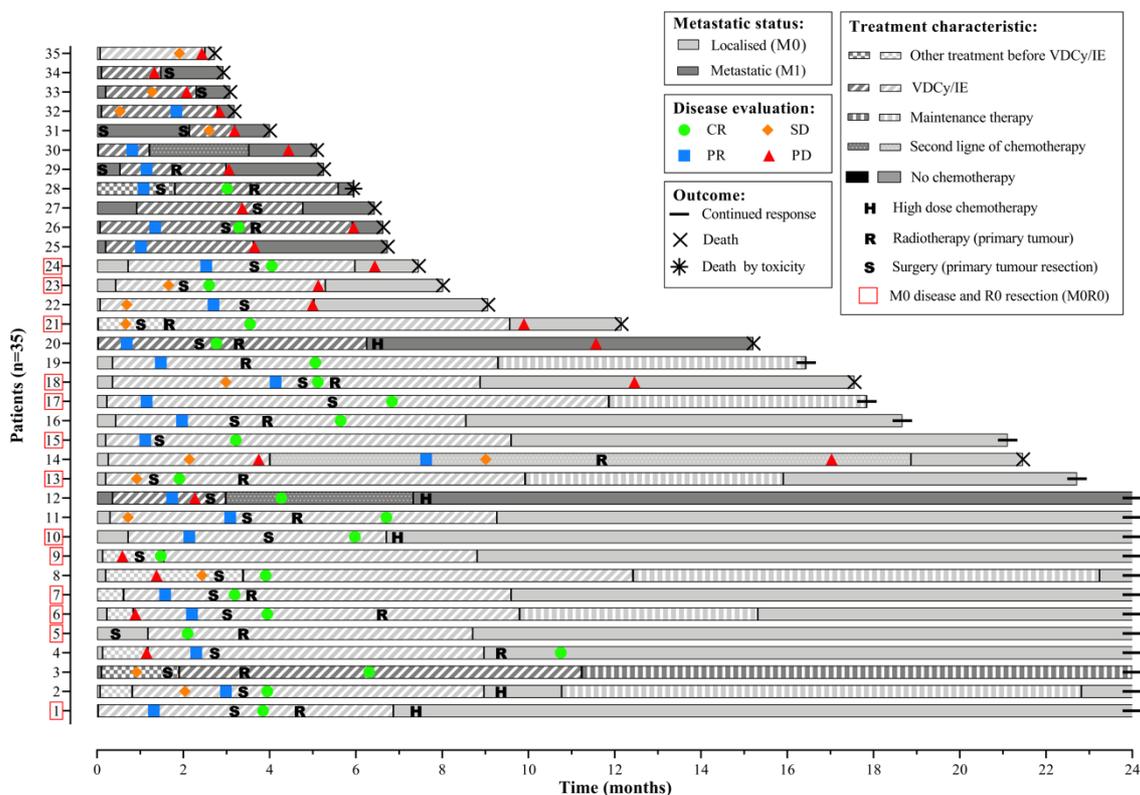
Cy: cyclophosphamide; D: doxorubicin; E: etoposide; I: ifosfamide; NS: not significant; SEM: standard error of the mean; V: vincristine.

Figure 4 - Local treatment of patients treated by VDCy/IE (n=35)



A. Extent of the surgical resection according to the localization of the primary tumour. **B.** Median interval between diagnosis and surgical resection of the primary tumour was 82 days (0 – 166). *It was lower ($p = 0.03$) for renal tumours (RTK; 50 days) than soft parts tumours (89 days) and hepatic tumours (103.5 days). **C.** Realization or lack of radiotherapy according to the age of the patient at diagnostic. **D.** Median doses in gray (Gy) of radiotherapy was 35.2 Gy (10.8 – 56); 25.4 Gy for RTK, 19.5 Gy for hepatic tumours and 54.0 Gy for soft parts tumours. **E.** Median interval between diagnosis and radiotherapy was 111 days (51 – 356); 103 days for RTK, 112 days for hepatic tumours and 142 days for soft parts tumours. NS: not significant; $p < 0.05$ (*).

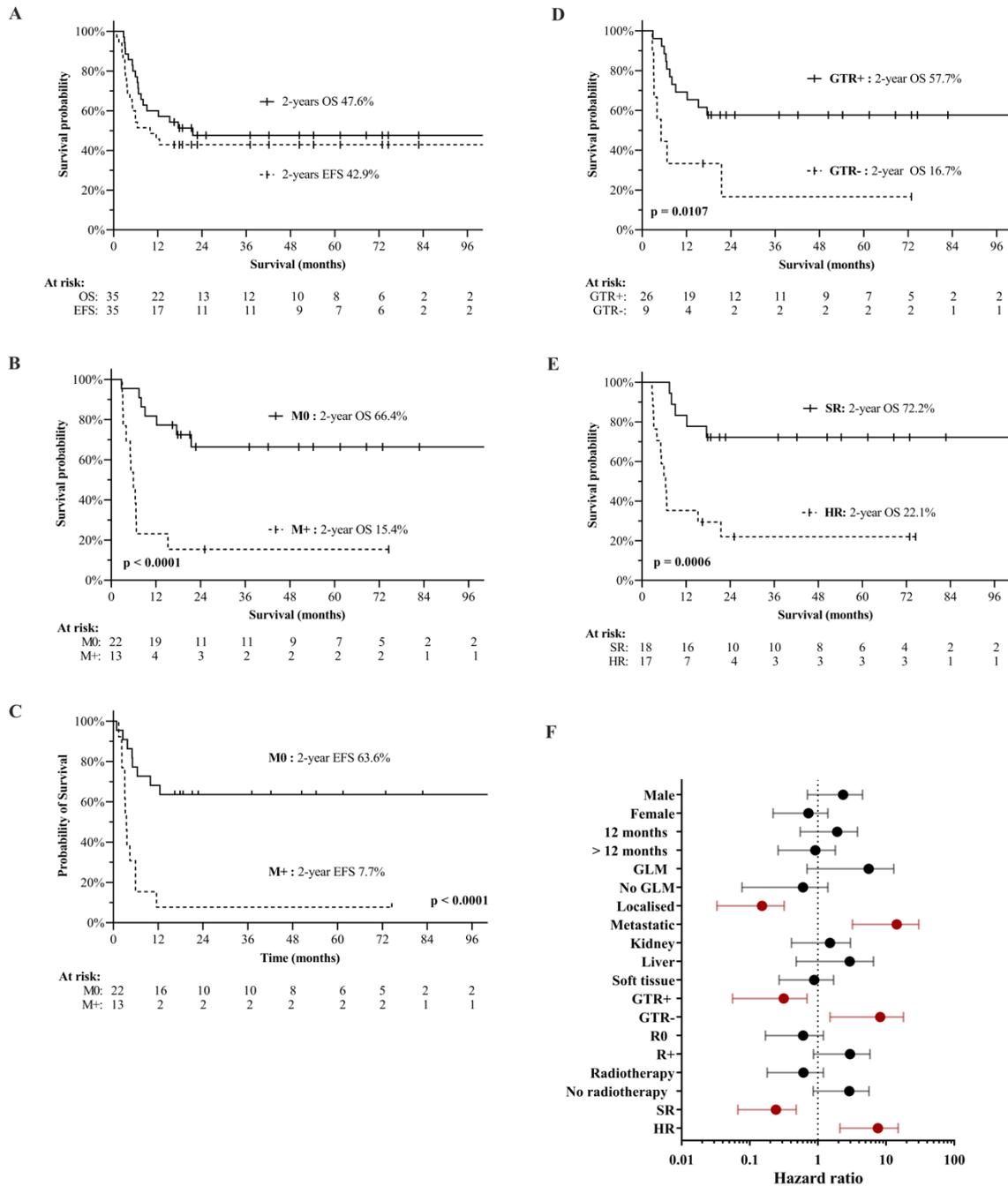
Figure 5 - Swimmer plot of patients treated by VDCy alternating with IE every two weeks (n=35)



Nine patients received other type of chemotherapy in first line before VDCy/IE because of an incorrect initial diagnosis (patients n°2, 3, 4, 6, 8, 21, 28), a spinal cord compression at diagnosis (n°7) or a very young age (n°9). The primary tumour was located in the kidney (n°3, 4, 5, 12, 13, 20, 21, 27, 28, 29, 34), in the liver (n°2, 17, 22, 25, 26, 32) or in miscellaneous soft parts (n° 1, 6, 7, 8, 9, 10, 11, 14, 15, 16, 18, 19, 23, 24, 30, 31, 33, 35). Progressions were tumour site only (n°14, 18), lymph node only (n°6), metastatic only (12, 20, 21, 24, 26, 29, 32, 33, 35) or both metastatic and tumour site (n° 22, 23, 25, 27, 30, 31, 34). All deaths were disease-related except patient n°28 who died after the bi-pulmonary irradiation.

CR: complete response; IE: ifosfamide, etoposide; PD: progressive disease; PR: partial response; SD: stable disease; VDCy: vincristine, doxorubicin, cyclophosphamide.

Figure 6 - Estimated 2-year survival and hazard ratio of patients treated by VDCy/IE (univariate analysis)



A. The 2-year OS was 47.6% (95% CI 30.2 – 63.1), while the 2-year EFS was 42.9% (95% CI 26.5 – 58.3). **B.** The 2-year OS was 15.4% (95% CI 2.5 – 38.8) for patients with metastatic disease (M+) at diagnosis and 66.4% (95% CI 41.7 – 82.5) for patients with localized disease (M0) with or without loco-regional lymph node involvement. **C.** The 2-year EFS was 7.7% (95% CI 0.7 – 29.2) for patients with metastatic disease (M+) at diagnosis and 63.6% (95% CI 40.3 – 79.8) for patients with localized disease (M0) with or without loco-regional lymph node involvement. **D.** The 2-year OS was 57.7% (95% CI 36.8 – 73.9) for patients who achieved gross total resection (GTR+) and 16.7% (95% CI 1.5 – 49.3) for those with incomplete resection (GTR-). **E.** The HR

group was characterized by patients presenting with one of the three pejorative factors (M+ and/or GTR- and/or GLM+). The SR group containing patients with absence of all three negative prognostic factors (M0 and GTR+ and GLM-). The 2-year OS was 22.1% (95% CI 6.2 – 44.2) for HR group and 72.2% (95% CI 45.6 – 87.4) for SR group. **F.** Forest plot of hazard ratio of OS.

CI: confidence interval; EFS: event free survival; HR: high risk; OS: overall survival; SR: standard risk.

APPENDICES

Appendix 1. Surgery treatment according to EpSSG recommendations

Primary Surgery of Rhabdoid Tumours

The recommendations for primary surgery of renal tumours are described in the SIOP Wilms tumour protocol - SIOP WT 2001. Tumour banking for all resected tumour specimens should be done as per individual tumour banking protocols.

Delayed surgical management of initially unresectable tumours

Patients should receive 11 weeks of preoperative chemotherapy followed by the appropriate imaging and surgery to resect residual tumour at week 13.

Definition of Unresectable tumours

- Tumour thrombus extending into the IVC above the level of the hepatic veins
- Tumours that involve contiguous structures whereby the only means of removal would involve removal of the contiguous structure (excluding the adrenal gland)
- Tumours that would result in tumour spillage if resected before chemotherapy
- Patients with pulmonary compromise due to extensive pulmonary metastases

Surgical management of metastases

Intra-abdominal metastases

If residual intra-abdominal metastatic disease remains after 11 weeks of chemotherapy, it should be resected if feasible. If complete resection is not feasible, then continue chemotherapy until week 25, assessing resectability at that point.

Pulmonary metastases

If residual pulmonary metastases remain after 11 weeks of chemotherapy, they should be resected if feasible. If not feasible resection after assessment at week 25 should be attempted.

Bone Metastases

Surgery is rarely recommended for boney metastases and should only be considered if results in resection of all known disease. Radiation is recommended instead.

Brain Metastases

Surgical resection of brain metastases may be considered before chemotherapy if feasible.

Cerebral tumors may sometime be considered as multifocal primaries, in a context of constitutional INI -1 mutation, in the overall therapeutic strategy.

Surgical Management of Extra-renal rhabdoid tumour

Extra-renal rhabdoid tumours can be found in a variety of locations including soft tissues of the trunk, the extremities, head and neck, abdomen, pelvis and retroperitoneum, as well as a variety of organs – thymus, liver, heart and bladder. The same general surgical principles apply as those to rhabdoid tumours occurring in the kidney i.e. complete surgical resection at diagnosis unless this is associated with significant morbidity – resection of organs or amputations - adjuvant chemotherapy should then be given to shrink the tumour with reassessment and possible surgery at week 13 or if still not feasible assessment and surgery at week 25.

Appendix 2. Chemotherapy schedule and drug doses according to EpSSG recommendations

Week number													
1	3	5	7	9	11	13	15	17	19	21	23	25	27
V	I	V	I	V	I	V	I	V	I	V	I	V	I
D	E	D	E	D	E	D	E	D	E	Cy	E	Cy	E
Cy		Cy		Cy		Cy		Cy					
V	Vincristine			0.025mg/kg/day IV x 1 as bolus for infants < 12 months 0.05mg/kg/day IV x 1 as bolus for children 12 months - 3 years 1.5 mg/m ² /day x1 as bolus for children ≥ 3 years old									
D	Doxorubicin			1.25mg/kg/day IV x 2 days over 15 minutes for infants <12 months or < 10 kg 37.5mg/m ² /day IV x 2 days over 15 minutes for children ≥ 12 months									
Cy	Cyclophosphamide			40 mg/kg/day IV x 1 day over 1 hour for infants < 12 months or < 10 kg 1200 mg/m ² /day IV x 1 day over 1 hour for children ≥ 12 months									
I	Ifosfamide			900 mg/m ² /day IV over 1 hour x 5 days for infants < 12 months or < 10 kg 1800 mg/m ² /day IV over 1 hour x 5 days for children ≥12 months									
E	Etoposide			3.3mg/kg/day IV over 1 hour x 5 days for infants < 12 months or < 10 kg 100mg/m ² /day IV over 1 hour x 5 days for children ≥ 12 months									

Chemotherapy in infants should be delivered very carefully and increased following patients' age and height. It may be considered to administer first cycle with reduced doses and increase them according to the toxicity in the subsequent courses.

Suggested starting dose for infants < 6 month or < 5 kg:

Vincristine = 0.025mg/kg/day IV x 1 as bolus

Doxorubicin = 62.5 µg/kg/day IV x 2 days over 2 – 4 hours

Cyclophosphamide = 20 mg/kg/day IV x 1 day over 1 hour

Ifosfamide = 450 mg/m²/day IV over 1 hour x 5 days

Etoposide = 1.65 mg/kg/day IV over 1 hour x 5 days

Administration schedule for cycles VDCy at weeks 1, 5, 9, 13 and 17 and for cycles VCy at weeks 21 and 25

Drug	Route	Dose	Day(s)
Vincristine	IV over 1 minute	0.025mg/kg/day for infants < 12 months 0.05mg/kg/day for children 12 months - 3 years 1.5 mg/m ² /day for children ≥ 3 years old	1
Doxorubicin	IV over 15 minutes	1.25mg/kg/day for infants <12 months or < 10 kg 37.5mg/m ² /day for children ≥ 12 months Individual groups may prefer to infuse over 1 – 24 hours	1 - 2
Cyclophosphamide With MESNA hydration*	IV over 1 hour	40 mg/kg/day for infants < 12 months or < 10 kg 1200mg/m ² /day for children ≥ 12 months	1

*Mesna and hydration guidelines: MESNA 1440 mg/m²/dose (48mg/kg/dose for infants <12 months old) should be added to the hydration (2000ml/m²/16 hours) of 0.45% saline/2.5% dextrose and run for 3 hours pre- and with cyclophosphamide, and at least 12 hours post cyclophosphamide – total 16 hours. Urine output at least 3ml/kg/hour.

Administration schedule for cycles IE at weeks 3, 7, 11, 15, 19, 23 and 27

Drug	Route	Dose	Day(s)
Ifosfamide With MESNA hydration*	IV over 1 hour	900 mg/m ² /day IV for infants < 12 months or < 10 kg 1800 mg/m ² /day IV for children ≥12 months	1 - 5
Etoposide	IV over 1 hour	3.3 mg/kg/day for infants < 12 months or < 10 kg 100 mg/m ² /day for children ≥ 12 months	1 - 5

*Hydration: prehydrate with 0.45 % saline/ 2.5 % dextrose at 125 ml/m²/hour for 2 hours. Then continue at 125ml/m²/hr for 2 hours following completion chemotherapy- total fluids 3000 ml / m²/d with 2200 mg/m² (1100 mg/m² for infants < 12 months) of MESNA added over 24 hrs after the last ifosfamide dose administration.

Appendix 3. Radiotherapy guidance according to EpSSG recommendations

Renal Rhabdoid Tumours

Indications for post-operative flank radiotherapy

Stage I-III renal rhabdoid tumour (19.8 Gy in 11 fractions of 1.8 Gy over 2 weeks for patients \geq 12 months; 10.5 Gy in 7 fractions of 1.5 Gy over 9 days for patients $<$ 12 months)

Indications for whole abdominal and pelvic radiotherapy

Stage III with cytology positive ascites

Preoperative intraperitoneal rupture

Diffuse operative spill and peritoneal seeding

(19.5 Gy in 13 fractions of 1.5 Gy over 17 days for patients \geq 12 months; 10.5 Gy in 7 fractions of 1.5 Gy over 9 days in the case of patients $<$ 12 months)

Indications for pulmonary radiotherapy

Lung metastases (15 Gy with lung correction in 10 fractions of 1.5 Gy over 12-14 days for patients \geq 12 months; 10.5 Gy in 7 fractions of 1.5 Gy over 9 days for patients $<$ 12 months)

Indications for liver radiotherapy

Liver metastases (19.8 Gy in 11 fractions of 1.8 Gy for patients \geq 12 months; 15 Gy in 10 fractions of 1.5 Gy for patients $<$ 12 months.)

Indications for whole brain radiotherapy

Brain metastases (21.6 Gy in 12 fractions of 1.8 Gy) + boost of 10.6 Gy

Indications for bone metastases radiotherapy

Bone metastases (25.2 Gy in 14 fractions of 1.8 Gy)

Timing of Radiation therapy

All radiation therapy should begin as soon as it is logistically possible concurrent with the initiation of chemotherapy after surgery which is either upfront or after 12 weeks of chemotherapy.

Extra-Renal Non-CNS Rhabdoid Tumour

All patients should have a consultation by a radiation oncologist at the time of study entry so that the radiation oncologist can assist in providing appropriate staging/grouping of the patient and review the adequacy of the initial diagnostic imaging studies for subsequent local control treatment with RT.

Gross total resection with no residual disease (microscopic negative margins) (Group I)	36 Gy in 20 fractions
Gross total resection with microscopic residual disease (microscopic positive margins) (Group II)	45 Gy in 25 fractions
Biopsy only or gross residual disease (Group III)	50.4 Gy in 28 fractions

Timing of Radiotherapy

All patients who require radiation therapy shall begin treatment concurrent with the initiation of chemotherapy after surgery. If surgery is performed up-front, radiation therapy should begin as close to the beginning of chemotherapy as possible. If surgery is delayed, radiation therapy should begin after recovery from surgery when chemotherapy is reinitiated. Chemotherapy will be given concurrent with radiotherapy. The regimen is designed so that doxorubicin is avoided during the six weeks following irradiation.