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Clinical Trial

Outcome of extracranial malignant rhabdoid tumours in children registered in the European Paediatric Soft Tissue Sarcoma Study Group Non-Rhabdomyosarcoma Soft Tissue Sarcoma 2005 Study—EpSSG NRSTS 2005

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Abstract ***Background:*** Extracranial malignant rhabdoid tumours (MRT) are rare lethal childhood cancers that often occur in infants and have a characteristic genetic mutation in the *SMARCB1* gene. The European Paediatric Soft Tissue Sarcoma Study Group (EpSSG) conducted a multinational prospective study of registered cases of extracranial MRT to test an intensive multimodal approach of treatment for children with newly diagnosed extracranial MRT.

Methods: Between December 2005 and June 2014, we prospectively registered 100 patients from 12 countries with a diagnosis of MRT tumour at an extracranial site on the EpSSG Non-Rhabdomyosarcoma Soft Tissue Sarcoma 2005 Study (NRSTS 2005). They were all treated on a standard multimodal protocol of surgery, radiotherapy, and chemotherapy over 30 weeks as follows: vincristine, cyclophosphamide, and doxorubicin (VDCy) at weeks 1, 10, 13, 22, and 28; vincristine was also given alone on weeks 2, 3, 11, 12, 14, 15, 23, 24, 29, and 30.

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Cyclophosphamide, carboplatin, and etoposide (Cy*CE) was given at weeks 4, 7, 16, 19, and 25. Radiotherapy was recommended for all primary tumour sites and all sites of metastatic disease.

Results: Forty-three patients completed the protocol treatment. Median follow-up for alive patients of the complete cohort was 44.6 months (range 11.5–84.6). For the whole cohort, the 3-year event-free survival (EFS) was 32.3% (95% confidence interval [CI] 23.2–41.6%) with a 3-year overall survival (OS) of 38.4% (95% CI 28.8–47.9%). For localised disease, the 4-year EFS was 39.3% (95% CI 28.2–50.1%) with a 4-year OS of 40.1% (95% CI 28.4–51.5%). For metastatic disease, the 2-year EFS was 8.7% (95% CI 1.5–24.2%) with a 2-year OS of 13.0% (95% CI 3.3–29.7%). Multivariable analysis disclosed that all patients ≤1 year of age were associated with at higher risk of death (hazard ratio [HR]: 2.6; 95% CI 1.0–6.8; p-value = 0.0094). Risk of death was also related with gender in metastatic patients (HR for males: 2.9, 95% CI 1.0–8.0; p-value = 0.0077).

Conclusions: The EpSSG NRSTS 2005 protocol of intensive therapy can be delivered to extracranial MRT patients, with a possible improvement in outcome. The outcome, however, remains poor for patients who progress or with metastatic disease.

1. Introduction

Extracranial MRT tumours are rare and often occur in infants with an age standardised incidence ratio of 0.6 per million children in the United Kingdom (UK), 61% of cases in the first of year of life [1]. The vast majority contain a somatic bi-allelic inactivating mutation in the *SMARCB1* gene, which is part of the chromatin remodelling complex SW1/SWF, important in cell cycle control, and functions as a classic tumour suppressor gene [2]. MRT are often described as lethal, with little evidence of improved survival in recent years. In the UK population-based National Registry of Childhood Tumours during 1993 to 2010, the 1-year overall survival (OS) was only 31% [1]. This poor survival is also reflected in the National Wilms' Tumour Study (NWTS) series, and in the United States, Surveillance Epidemiology and End Results (SEER) programme, OS, at 4 years was 23.3% and 33.0%, respectively [3,4]. Given the rarity of extracranial MRT, there is no standard therapeutic pathway, and there has been no randomised or prospective trials examining the role of chemotherapy combinations or, indeed, the addition of new agents. Instead, there have been small retrospective series published either from single institutions or larger series of MRT at single anatomical sites from other site-specific studies, such as NWTS [3,5]. Despite the challenging nature of this tumour and its treatment, two case reports including two and one patients, respectively, with metastatic renal MRT are often cited in view of their successful outcome [6,7]. Based on these reports, the European Paediatric Soft Tissue Sarcoma Study Group (EpSSG) conducted a multinational prospective study of registered cases of extracranial MRT to test an intensive multimodal approach of treatment for children with newly diagnosed extracranial MRT.

2. Methods

2.1. Patients and study design

One hundred patients with a diagnosis of MRT at an extracranial site were registered on the EpSSG Non-Rhabdomyosarcoma Soft Tissue Sarcoma 2005 Study (NRSTS 2005). This was a prospective observational study for all NRSTS patients, with recommended treatment for MRT. The study was conducted in accordance with the Declaration of Helsinki and the Good Clinical Practice guidelines. Informed written consent was obtained for all patients/parents. The study was managed via a Web-based system provided by CINECA, an Inter-University Computing Consortium (Casalecchio, Italy).

2.2. Pathological analysis

National and international review by the pathology panel of the histological diagnosis was advised but not considered mandatory. Patients were included if their local histological diagnosis of MRT was supported by immunohistochemistry demonstrating loss of nuclear expression of INI-1 (BAF47 antibody) and/or molecular testing demonstrated deletion of the *SMARCB1* gene [2]. Additional national and/or an international review by the EpSSG panel of pathologists were performed in 64 of the cases.

2.3. Staging and surgery

Following staging investigations, including either computed tomography (CT) or magnetic resonance imaging (MRI) of the primary site, CT scan chest, MRI/CT scan of brain, and for some bone scan and bone marrow assessment, it was recommended for all patients

to undergo surgical resection of primary tumour but if deemed unresectable, biopsy only. The Intergroup Rhabdomyosarcoma Study (IRS) and TNM post-surgical staging was used [8]. Complete resection with no microscopic disease was R0, with microscopic disease was R1, and macroscopic disease was R2.

2.4. Chemotherapy

Following initial surgery or biopsy, the recommended chemotherapy was given over 30 weeks as follows: vincristine, cyclophosphamide, and doxorubicin (VDCy) at weeks 1, 10, 13, 22, and 28; vincristine was also given alone on weeks 2, 3, 11, 12, 14, 15, 23, 24, 29, and 30; cyclophosphamide, carboplatin, and etoposide (Cy*CE) given at weeks 4, 7, 16, 19, and 25 (see Appendix 1 for full dose and schedule plan). Dosages were adapted to infant weight and progressively increased. No details about doses of chemotherapy were collected, but data were available on whether treatment was received and if completed.

2.5. Radiotherapy

Radiotherapy was recommended for all primary tumour sites and all sites of metastatic disease, either following up-front surgery at week 2 or following delayed surgery at week 14. The chemotherapy schedule allowed concomitant radiotherapy. The dose up to a maximum of 50.4 Gy, treatment volume, and fractionation depended on the site of the primary tumour, degree of resection, site, and type of metastases (Appendix 2 for full details).

2.6. Toxicity and disease evaluation

Severe toxicity and serious adverse events were recorded on the end of treatment form but as a registry this was not graded according to the National Cancer Institute Common Toxicity Criteria.

If no signs of tumour progression were present, a formal tumour revaluation was advised at the end of treatment in patients without measurable disease and after 12 weeks of chemotherapy in patients with measurable disease, including those patients with metastases.

2.7. Statistical analyses

Data were collected via a web-based system and analysed at Istituto Oncologico Veneto (Padua, Italy) considering information reported up to 27th May 2015. Continuous variables were summarised with median, minimum and maximum, and categorical variables were reported as counts and percentages. Survival time was calculated from the date of diagnosis to the time of event or last follow-up. Tumour progression, relapse or death due to any causes were considered for event-free survival (EFS). OS was measured from the date of diagnosis to death for any reason. Patients still alive at the end of the study were censored at the date of last observation. The survival probability was computed by means of the Kaplan–Meier method and heterogeneity in survival among strata of selected variables was assessed through the log-rank test. The 3-year EFS and OS (4-year EFS for localized tumours) were reported along with their 95% confidence intervals (CIs). To investigate the impact of the variables gender, age category ($\leq$1 year; >1 year), tumour size ($\leq$5 cm; >5 cm), primary site (favourable: orbit, head and neck non-parameningeal, genitourinary non-bladder–prostate; unfavourable: parameningeal, bladder-prostate, extremities, "other"; according to rhabdomyosarcoma classification, IRS group and initial surgery (performed; not performed) on EFS for localized patients and OS for localized and metastatic patients, survival multivariable analysis were conducted using the Cox proportional hazard regression method [8]. A stepwise variable selection procedure was applied to the covariates with a p-value of at least 0.05 at univariate analysis. Hazard ratios (HRs) with their 95% CI calculated according to the Wald method was reported for significant variables. To check the proportional hazards assumption, a score process (which is a transformed partial sum process of the martingale residuals) was compared with the simulated processes under the null hypothesis that the proportional hazards assumption holds [14]. All data analyses were performed using the SAS statistical package (SAS, release 9.4; SAS Institute Inc, Cary, NC).

3. Results

3.1. Patients

Between December 2005 and June 2014, 110 patients were enrolled on the study but 10 were excluded due to adherence to other protocols (3), immunohistochemistry and molecular data missing (1), histological diagnosis after pathology review was not MRT (2) or immunohistochemistry did not demonstrate loss of nuclear expression of INI-1, and/or molecular testing did not demonstrate deletion of the *SMARCB* gene (4), leaving in total 100 eligible patients. There was an even distribution between the sexes, 49 female and 51 male. The median age at diagnosis was 1.4 years (range 3 d–10.9 years) with 41 patients $\leq$1 year of age. The majority (56 patients) were between 2 and 9 years (39 patients between the ages 1 and 3 years) and only 3 were older than 10 years. Patient staging data and site and size of primary tumour are listed in Table 1. The majority in the series had localised disease (77 patients) and of those 19 (25%) had surgical resection up front. The primary site of the tumour was across multiple

Table 1
Clinical characteristics.

	Localised patients, N = 77	Metastatic patients, N = 23	Total	Total %
Age (years) at diagnosis				
Median (min–max)	1.51 (0.01–10.93)	0.60 (0.01–0.60)	1.38 (0.01–10.93)	
≤1	29	12		41
>1	48	11		59
Gender				
Female	35	14		49
Male	42	9		51
Post-surgical tumour staging (IRS)				
Group I	7	–		7
Group II	12	–		12
Group III	58	–		58
Group IV	–	23		23
Primary tumour Invasiveness (T)				
T0—no detectable	–	1		1
T1—localized to the organ or tissue of origin	34	6		40
T2—extending beyond the tissue or organ of origin	42	14		56
Tx—insufficient information about the primary tumour	1	2		3
Tumour size				
a: ≤5 cm	19	3		22
b: >5 cm	56	19		75
X: not evaluable	2	1		3
Regional lymph node involvement				
N0—No evidence of lymph node involvement	67	10		77
N1—Evidence of regional lymph node involvement	9	11		20
Nx—No information on lymph node involvement	1	2		3
Site of origin of primary tumour				
Orbit	1	–		1
Head neck	12	–		12
Parameningeal	7	–		7
Bladder-prostate	4	–		4
Genitourinary non-Bladder–prostate	11	7		18
Kidney	*10*	*7*		*94*
Uterus	1	–		5
Extremities	8	6		14
Other sites	34	10		44
Abdomen	*2*	–		*2*
Liver	*10*	*5*		*15*
Paraspinal	*13*	*1*		*14*
Pelvis	*1*	–		*1*
Perineum	*1*	–		*1*
Retroperitoneal	–	*2*		*2*
Thorax	*6*	*2*		*8*
Trunk	*1*	–		*1*
Number of metastatic sites[a]				
1	–	9		39
2	–	8		35
3	–	3		13
4	–	3		13

IRS, Intergroup Rhabdomyosarcoma Study; max, maximum; min, minimum.

[a] Percentage computed considering metastatic patients only.

anatomical sites, the commonest site in this series was "other" sites (44 patients) followed by genitourinary non-bladder–prostate (18 cases).

Twenty-three patients had distant metastases. The majority (17 patients) had metastases to the lung: four patients lung alone and 13 with other metastases. Two cases had brain tumour metastases. Thirteen patients had congenital MRT as defined by diagnosis within the first 4 weeks of birth. Five of them (39%) had metastatic disease, with the majority having tumours greater than 5 centimetres (62%). Primary sites were multiple but the largest group was "other"—paraspinal, thorax, retroperitoneal or liver. One case had brain tumour metastases.

3.2. Treatment and toxicity

Forty-three patients completed the protocol treatment in a median period of 8.4 months (minimum 6.5–maximum 13.0) of chemotherapy. Fifty-five patients discontinued chemotherapy due to toxicity (3), early progressive disease (49) between 3 d and 10.9 months or physician's choice (3). One patient did not receive any treatment due to death before starting treatment and for one patient no treatment data are available. There were dose adjustments due to delays in starting the next course of chemotherapy or mucositis in 10 patients. The most frequent reported toxicities included bone marrow suppression, febrile neutropenia, infection, mucositis, anorexia, and electrolyte disturbances. In those who completed all courses of chemotherapy, there were no permanent toxicities, such as renal impairment, and there were no toxic deaths. All those younger than 12 months were able to receive chemotherapy except one patient who died before the start of treatment. They were no more likely to have toxicities than older patients but had doses of chemotherapy adjusted for their age and weight.

Fifty-four patients from the whole cohort did not receive radiotherapy, 39 had progressive disease during first-line treatment prior to the planned radiotherapy, whereas in 15 patients, no radiotherapy was delivered by physicians choice probably due to the very young age of the patient. One patient developed radiation colitis but there were no other radiation-recorded toxicities. For the localised patients, 25 progressed before planned radiotherapy with only 37 of the remaining 52 patients receiving radiotherapy.

Up-front complete surgical resection of the primary tumour was performed in 8 (R0 resection), including 1 metastatic patient, and in 12 patients R1 resection. In 73, only a surgical/trucut biopsy or lymph node exploration was performed at diagnosis (53 localised and 20 metastatic patients). For the remaining seven patients, macroscopic tumour was present after surgical resection of primary tumour (five localised and two metastatic patients). Thirty-nine patients had second surgery, for

26 after 3–4 cycles of chemotherapy, for 8 after 5–8 cycles and for 3 at another time. Additional surgeries were necessary for two patients. This resulted in a 17 with a R0 resection including 1 with a liver transplant, R1 resection in 13, and macroscopic residual tumour in 8. In one case, no tumour was found.

3.3. Outcome data

Median follow-up for alive patients of the complete cohort was 44.6 months (range 11.5–84.6), for localized patients was 49.8 months (range 11.5–84.6), whereas for metastatic patients was 32.1 months (range 14.9–38.8). Sixty-seven patients developed an event (46 in localized and 21 metastatic patients) and subsequently 65 died (45 in localized and 20 metastatic patients). Median time to progression was 5.0 months (minimum 3 d, maximum 31.5 months), for localised patients 7.5 months (1.4–31.5) and for metastatic patients 2.7 months (3 d–14.9 months). In the total cohort, 35 were alive at the time of this analysis.

For the whole cohort, the 3-year EFS was 32.3% (95% CI 23.2–41.6%) with a 3-year OS of 38.4% (95% CI 28.8–47.9%; Fig. 1A and B). For localized disease, the 4-year EFS was 39.3% (95% CI 28.2–50.1%) with a 4-year OS of 40.1% (95% CI 28.4–51.5%; Fig. 1C and D). For metastatic disease, the 2-year EFS was 8.7% (95% CI 1.5–24.2%) with a 2-year OS of 13.0% (95% CI 3.3–29.7%; Fig. 1C and D). For IRS III disease, achieving a complete response (CR) at any time point occurred in 30 patients leading to a statistically significant ($p<0.0001$) survival advantage with a 4-year EFS of 66.3% (95% CI 46.5–80.3%) and 4-year OS of 66.8% (95% CI 44.6–81.7%) compared with no CR in 28 patients with a 4-year EFS of 4.8% (95% CI 0.4–18.9%) and 4-year OS of 4.8% (95% CI 0.4–18.9%).

3.4. Prognostic factors

Table 2 lists the estimated EFS and OS for the patient's clinical characteristics in those with localized tumours. On univariate analysis, patient age only significantly influenced the EFS and OS, with those ≤1 year of age having a significantly worse outcome, with a 4-year EFS of 17.2% (95% CI 6.3–32.7%) and an HR of 2.9 (95% CI 1.6–5.3) and a 4-year OS of 20.1% (95% CI 7.9–36.3%) with an HR of 2.7 (95% CI 1.5–5.0). Table 3 lists the estimated 1-year OS by main characteristics of

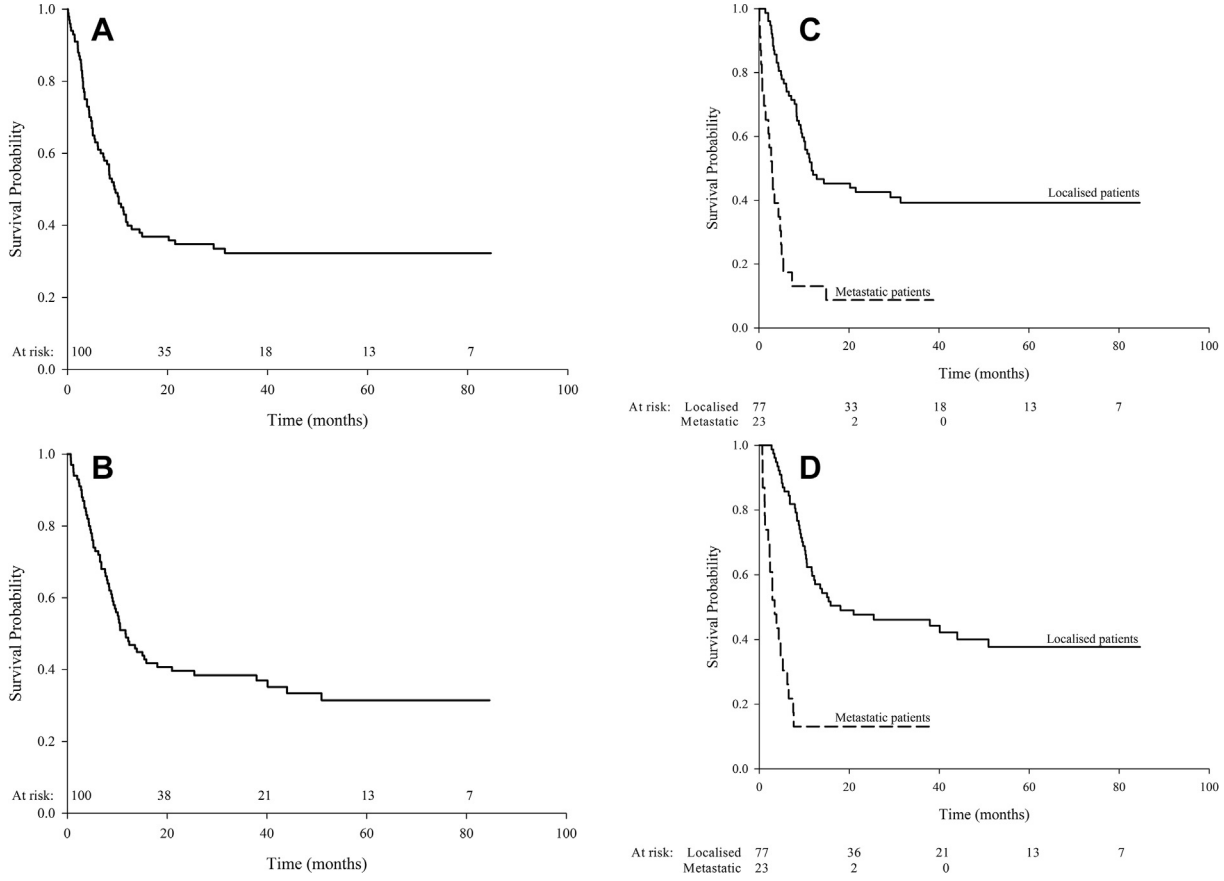

Fig. 1. Survival analysis of whole cohort, localised and metastatic extracranial MRT. (A) Event-free survival and (B) overall survival of 100 patients with extracranial MRT registered on EpSSG NRSTS 2005. (C) Event-free survival and (B) overall survival of localised and metastatic patients separately.

Table 2
Estimated EFS and OS for localised patients (univariate analysis).

Characteristics	N	No. events EFS	1-Year EFS (95% CI)	4-Year EFS (95% CI)	*p*-Value	No. events OS	1-Year OS (95% CI)	4-Year OS (95% CI)	*p*-Value
IRS group					0.2961				0.3234
I	7	2	85.7 (33.4–97.8)	68.6 (21.3–91.2)		2	85.7 (33.4–97.8)	68.6 (21.3–91.2)	
II	12	8	41.7 (15.2–66.5)	33.3 (10.3–58.8)		8	75.0 (40.8–92.2)	41.7 (15.2–66.5)	
III	58	36	44.8 (31.8–57.0)	36.9 (24.4–49.4)		35	53.4 (39.9–65.2)	35.9 (22.7–49.3)	
Age at diagnosis (years)					0.0002				0.0005
≤1 year	29	24	24.1 (10.7–40.5)	17.2 (6.3–32.7)		23	34.5 (18.2–51.4)	20.1 (7.9–36.3)	
>1 year	48	22	62.4 (47.2–74.4)	52.8 (37.5–66.1)		22	75.0 (60.2–85.0)	52.1 (35.7–66.2)	
Gender					0.6600				0.6288
Male	42	23	45.0 (29.6–59.2)	45.0 (29.6–59.2)		23	61.8 (45.4–74.6)	45.6 (29.5–60.4)	
Female	35	23	51.4 (34.0–66.4)	33.3 (18.3–49.1)		22	57.1 (39.3–71.5)	33.4 (17.4–50.3)	
T[a]					0.2193				0.1196
T0–T1	34	17	55.7 (37.6–70.5)	49.3 (31.6–64.8)		16	64.6 (46.1–78.1)	52.4 (32.7–68.9)	
T2	42	28	42.8 (27.8–57.0)	32.6 (19.0–47.0)		28	57.1 (40.9–70.4)	31.9 (18.2–46.5)	
Size[a] (cm)					0.6555				0.6671
≤5	19	10	52.6 (28.7–71.9)	47.4 (24.4–67.3)		10	63.2 (37.9–80.4)	47.4 (24.4–67.3)	
>5	56	34	48.1 (34.5–60.4)	37.4 (24.4–50.3)		33	60.6 (46.6–72.0)	38.0 (24.0–51.9)	
Site					0.2765				0.3525
Favourable	24	12	57.8 (35.7–74.7)	48.9 (27.8–67.0)		12	75.0 (52.6–87.9)	52.3 (30.4–70.2)	
Unfavourable	53	34	43.3 (29.9–56.1)	35.5 (22.8–48.3)		33	52.8 (38.6–65.1)	35.5 (22.3–48.9)	
Initial surgery					0.7451				0.8096
No	49	29	44.9 (30.7–58.1)	40.2 (26.4–53.7)		28	55.1 (40.2–67.7)	39.7 (24.9–54.1)	
Yes	28	17	53.3 (33.5–69.7)	37.2 (19.4–55.1)		17	67.7 (47.0–81.7)	40.0 (21.5–57.9)	

CI, confidence interval; EFS, event-free survival; IRS, Intergroup Rhabdomyosarcoma Study; OS, overall survival.
[a] The sum does not add up to the total because of missing values.

metastatic patients. Patients ≤1 year of age had the worst prognosis, as well as male patients. Multivariable analysis disclosed that all patients ≤1 year were associated with at higher risk of death (HR: 2.6; 95% CI 1.0–6.8; p-value = 0.0094). Risk of death was also related with gender in metastatic patients (HR for males: 2.9, 95% CI 1.0–8.0; p-value = 0.0077)

Table 3
Estimated OS for metastatic patients (univariate analysis).

Characteristic	N	No. events	1-year OS (95% CI)	*p*-Value
Age at diagnosis (years)				0.0094
≤1 year	12	12	0	
>1 year	11	8	27.3 (6.5–53.9)	
Gender				0.0077
Male	9	9	0	
Female	14	11	21.4 (5.2–44.8)	
T[a]				0.3709
T0–T1	7	7	0	
T2	14	11	21.4 (5.2–44.8)	
Size[a]				0.1913
≤5 cm	3	2	33.3 (9.0–77.4)	
>5 cm	19	17	10.5 (1.8–28.4)	
Site				0.6406
Favourable	7	7	0	
Unfavourable	16	13	18.8 (4.6–40.2)	
Initial surgery				0.4330
No	19	17	10.5 (1.8–28.4)	
Yes	4	3	25.0 (8.9–66.5)	

CI, confidence interval; OS, overall survival.
[a] The sum does not add up to the total because of missing values.

4. Discussion

Our results demonstrate that in this first large prospective study of extracranial MRT treated in multiple European countries for what is a very rare soft tissue sarcoma, intensive therapy can be delivered to a very young paediatric population of patients, with possibly an improvement in outcome, be it in comparison with historical series. Furthermore, a substantial proportion of the patients in this EpSSG protocol had an extra-renal tumour site, which confers a poorer prognosis [1]. The outcome remains poor for the majority of patients in this series, in particular patients with metastatic disease and those who progressed, who universally had a fatal outcome.

In the NWTS series of renal MRT, over a much longer historical period between 1969 and 2002, OS at 4-year was 23.2% [3]. This compares to, perhaps, our superior results with an OS of 38.4%, and perhaps, it is significant in terms of a better outcome, as the NWTS series only contained patients with a renal primary, thought to have a better outcome, maybe in part because a larger proportion can have up-front resection of the primary tumour. In our series, it is noteworthy that only 24% had up-front surgery with no survival advantage, and with surgery following chemotherapy 73% were in CR. CR, by either surgery or chemotherapy in IRS III patients, had a survival advantage but also reflects those patients who had not progressed before delayed local control and, therefore, must be read with caution. The role of a CR maybe important for

long-term survival as suggested in previous small series [11]. The small numbers with a concomitant CNS primary compared to the NWTS series reflect selection of these patients into CNS protocols rather than our study [3]. The small numbers also makes it hard to comment on therapy, but at present most will receive similar intensive chemotherapy, surgical resection if possible plus or minus radiation.

We showed that age continues to be an important prognostic factor and remains the only factor in multivariable analysis for OS in localised patients and univariate analysis for metastatic patients. The importance of age, in particular the negative effect of younger age on outcome, confirms the findings in the NWTS series [3], the SEER database series [4], and the UK population-based registry [1]. Uniquely, we analysed the congenital cases separately (13 cases) with 12 events (all died) and a median time to event of 3.1 months (3–11.7 d). It might be expected that these cases had a germline mutation of the *SMARCB1* gene, thought to confer a poorer prognosis, but our data are incomplete [12]. Their outcome may also question the role of intensive therapy in congenital cases or, indeed, in the very young cohort. For parents, however, offering palliative therapy as the first line of treatment may not be acceptable.

Progression on treatment remains an important finding, 49.5% progressed on treatment, which was an important factor for those subjects not receiving the recommended protocol radiotherapy. Of course, age of the patient may also be a further factor for no radiotherapy as in the 15 patients with physicians choice for no radiotherapy, 14 were younger than 2 years.

The role of radiotherapy as an important factor affecting outcome could not be shown in our series, confounded by the number who progressed prior to delivering radiotherapy and the reluctance to give radiotherapy to very young children especially in infants or with a planned delay. This echoes the findings of the NWTS series, as the possible benefit of radiotherapy again was difficult to define, and also confounded by the patient's age [3]. Radiotherapy tended to be given to those with a higher clinical stage and in an older age group, who received a higher dose. This is in contrast, however, to the SEER database series [4]. In particular where the use of radiotherapy remained a significant predictor of survival ($p = 0.0006$). Radiotherapy was only used in 35% of patients in total, but there was no significant difference in its use at the different primary tumour sites ($p = 0.90$). Less was used, however, in those younger than 3 years.

For localised disease, stage was not an important predictor of outcome but a statistically significant difference in EFS and OS is evident comparing localised with metastatic patients (p-value for log-rank test <0.0001 in EFS and OS). In both the NWTS series and the SEER database series, stage also determined outcome, with a 41.8% 4-year OS for stage I to II tumours compared with 15.9% in those with stage III, IV, or V disease in NWTS, and in for the SEER database series in a multivariable model applied only to children and adolescents with extracranial MRT, tumour stage remains a significant predictor of survival ($p = 0.00014$) [3,4].

Like any discussion comparing historical series, the staging systems used, the patient selection and the numbers at each anatomical site are not directly comparable and, hence, cannot replace a randomised study. The lack of prospective historical series in MRT at all sites hampers this further. Extracranial MRT continue to be aggressive tumours with poor survival. The young age at presentation often limits the ability to deliver multimodal therapy, in particular radiotherapy, which seems to be important. Further research needs to allow better understanding of MRT biology and the role of the *SMARCB1* gene in MRT development. The later information could also determine better and more targets for therapy. A recent eloquent study in the molecular subgroups of primary brain atypical teratoid rhabdoid tumours, biologically the same tumour, allowed further stratification of these tumours for future biologically based trials [10]. Our results may allow us to use this protocol as a standard chemotherapy backbone in order to add small molecule inhibitors against what we currently know are targets. Recent data on EHZ2 inhibitors is promising as an epigenetic regulator and should be in phase I studies shortly in children [13]. We may need to take a leap of faith based on cell line data and pre-clinical mouse models to put these agents into phase III clinical trials while not having data from phase II trials in MRT, as it is so rare, but at least toxicity data from phase I studies in paediatric tumours. We will not improve the outcome with this protocol which is already at maximal tolerance but we may alter how we deliver conventional chemotherapy as successfully demonstrated in the Ewings sarcoma study of interval compressed chemotherapy—AEWS0031 [9], with new targeted agents, to be given in combination, in a multiple arm randomised study using an innovative statistical plan for rare cancers.

Conflict of interest statement

None declared.

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Appendix 1. Chemotherapy schedule and drug doses for rhabdoid tumours registered on the EpSSG NRSTS 2005 study

Chemotherapy schedule

Week number

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30
V	V	V							V	V	V	V	V	V							V	V	V				V	V	V
D			Cy*			Cy*			D			D			Cy*			Cy*			D			Cy*			D		
Cy			C			C			Cy			Cy			C			C			Cy			C			Cy		
			E			E									E			E						E					

V	Vincristine	0.025 mg/kg/d i.v. × 1 as bolus for infants <12 months 0.05 mg/kg/d i.v. × 1 as bolus for children 12 months to 3 years 1.5 mg/m^2/d × 1 as bolus for children ≥3-year old
D	Doxorubicin	1.25 mg/kg/d i.v. × 2 d over 15 min for infants <12 months 37.5 mg/m^2/d i.v. × 2 d over 15 min for children ≥12 months
Cy	Cyclophosphamide	40 mg/kg/d i.v. × 1 d over 1 h for infants <12 months 1200 mg/m^2/d i.v. × 1 d over 1 h for children ≥12 months
Cy*	Cyclophosphamide	14.7 mg/kg/d i.v. over 1 h × 5 d for infants <12 months 440 mg/m^2/d i.v. over 1 h × 5 d for children ≥12 months
C	Carboplatin	See nomogram in protocol
E	Etoposide	3.3 mg/kg/d i.v. over 1 h × 5 d for infants <12 months 100 mg/m^2/d i.v. over 1 h × 5 d for children ≥12 months

Administration schedule for cycles VDCy weeks 1, 10, 13, 22 and 28

Drug	Route	Dose	Week (s)	Day(s)
Vincristine	i.v. over 1 min	0.025 mg/kg/d for infants <12 months 0.05 mg/kg/d for children 12 mo. to 3 years 1.5 mg/m^2/d for children ≥3-year old	1, 2, 3, 10, 11, 12, 13, 14, 15, 22, 23, 24, 28, 29, 30	1
Doxorubicin	i.v. over 15 min	1.25 mg/kg/d for infants <12 months 37.5 mg/m^2/d for children ≥12 months Consideration for the use of a cardioprotective agent. Individual groups may prefer to infuse over 1 h.	1, 10, 13, 22, 28	1–2
Cyclophosphamide with MESNA hydration[a]	i.v. over 1 h	40 mg/kg/d for infants <12 months 1200 mg/m^2/d for children ≥12 months	1, 10, 13, 22, 28	1

[a] MESNA and hydration guidelines: MESNA 1440/m^2/dose (48 mg/kg/dose for infants <12 months old) should be added to the hydration (2000 ml/m^2/16 h) of 0.45% saline/2.5% dextrose and run for 3 h pre- and with cyclophosphamide and at least 12 h post-cyclophosphamide—total 16 h. Urine output at least 3 ml/kg/h.

Administration schedule for cycles Cy*CE weeks 4, 7, 16, 19, and 25

Drug	Route	Dose		Week	Day(s)
Cyclophosphamide with MESNA hydration	i.v. over 1 h	14.7 mg/kg/d for infants <12 months 440 mg/m^2/d for children ≥12 months		4, 7, 16, 19, 25	1–5
Carboplatin	i.v. over 1 h	GFR	Dose	4, 7, 16, 19, 25	1
		>150 ml/min/1.73 m^2	560 mg/m^2 (18 mg/kg for infants)		
		100–150 ml/min/1.73 m^2	500 mg/m^2 (16.6 mg/kg for infants)		
		75–99 ml/min/1.73 m^2	370 mg/m^2 (12.3 mg/kg for infants)		
		50–74 ml/min/1.73 m^2	290 mg/m^2 (9.7 mg/kg for infants)		
		≤49 ml/min/1.73 m^2	Discuss with study coordinators		
Etoposide	i.v. over 1 h	3.3 mg/kg/d for infants <12 months 100 mg/m^2/d for children ≥12 months		4, 7, 16, 19, 25	1–5

Hydration: prehydrate with 0.45% saline/2.5% dextrose at 125 ml/m^2/h for 2 h. Then continue at 125 ml/m^2/h for 2 h following completion chemotherapy—total fluids 500 ml/ m^2 with 530 mg/m^2 of MESNA added.
i.v., intravenous; MESNA, 2-mercaptoethane sulfonate sodium.

Appendix 2. Radiotherapy guidance for the rhabdoid tumours registered on the EpSSG NRSTS 2005

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 15 d for patients $\geq$ 12 months; 10.5 Gy in 7 fractions of 1.5 Gy over 9 d for patients $<$ 12 months)

Indications for whole-abdominal and pelvic radiotherapy

- Stage III with cytology positive ascites
- Pre-operative intraperitoneal rupture
- Diffuse operative spill and peritoneal seeding (19.5 Gy in 13 fractions of 1.5 Gy over 17 d for patients $\geq$ 12 months; 10.5 Gy in 7 fractions of 1.5 Gy over 9 d in the case of infants)

Indications for pulmonary radiotherapy

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

- None 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 up front or after 12 weeks of chemotherapy.

Equipment

All patients will be treated with megavoltage equipment (4–20 MV linear accelerator. The use of colbalt-60 equipment is not acceptable for radical therapy.)

Treatment planning

All patients should have a planning CT scan to enable three-dimensional conformal planning, generation of dose volume histograms for organs at risk, and lung correction where necessary. The dose is prescribed according to international commission on radiation units and measurements (ICRU) 50.

Fractionation

Treatment is given with conventional fractionation, treating all fields each day, with one treatment daily, 5 d a week. The fraction size should be 1.8 Gy except with large fields (whole-abdominal and pelvic radiotherapy, and whole-lung irradiation) and in infants. Once treatment is started, there will be no interruptions in treatment unless absolutely necessary. It is not necessary to suspend treatment because of uncomplicated myelosuppression, supportive care should be given for neutropenia and thrombocytopaenia according to local protocols. Haemoglobin levels should be maintained at 12 g/dl or above during the time of radiotherapy.

►►► *Compensation for treatment breaks*

Standard fractionation is one treatment per day, 5 d each week. If a treatment interruption is unavoidable, this should be compensated for. Ideally, two fractions per day with a minimum interfraction interval of 6 h should be given to enable treatment to be completed within the same overall time as was originally intended. If this is not possible, for example in the case of a child requiring general anaesthesia, one or two additional fractions should be given according to the Children's Oncology Group (COG) guidelines below.

Or as per COG protocol

The total number of fractions or total radiotherapy dose to be delivered according to the duration of interruptions is indicated below:

Patients prescribed 10.8 Gy

Timing	Fx size	# Fx	Total dose (Gy)
Normal and/or up to 3-d split	1.8	6	10.8
4- to 7-d split	1.8	7	12.6
>7-d split	1.8	8	14.4

Patients prescribed 19.8 Gy

Timing	Fx size	# Fx	Total dose (Gy)
Normal and/or up to 3-d split	1.8	11	19.8
4- to 7-d split	1.8	12	21.6
>7-d split	1.8	13	23.4

Target volume definition for primary tumour

- The target volume is chosen according to the initial tumour volume (gross tumour volume [GTV]). The pre-therapeutic CT is usually the optimal imaging study.
- The clinical target volume (CTV) is defined as the GTV + 1 cm extended medially (and superiorly and inferiorly as appropriate) to encompass vertebral bodies in their entirety.
- The planning target volume (PTV) is defined as the CTV + 1 cm unless departmental quality control data indicate that a different margin is appropriate.

Flank irradiation

The GTV is determined by the pre-operative CT scan and it is defined as the outline of the kidney with the

associated tumour. The PTV should not extend more than 2 cm beyond the defined GTV, except where necessary to allow the superior and inferior field borders to lie within an intervertebral space, and the medial border to fully encompass the entire vertebral width without significantly overlapping the contralateral kidney. In patients where the tumour prior to resection bulged into the contra lateral flank without tumour invasion into the contra lateral kidney, it is not necessary for the CTV to encompass the medial extent of the GTV, and so the PTV can lie so that the full vertebral width is covered without overlap of the contralateral kidney. In most patients, the superior border of the radiation therapy field will be well below the diaphragmatic dome. The radiation therapy field should not be extended to the dome of the diaphragm unless there is tumour extension to that height. When there are positive lymph nodes that have been surgically removed, the entire length of the para-aortic chain of lymph nodes should be included in the radiotherapy field. An anteroposterior parallel-opposed (AP-PA) technique is recommended for flank irradiation. The borders of the radiation fields should be placed so that the PTV is encompassed by the 95% isodose. The flank irradiation dose is 19.5 Gy in 13 fractions of 1.5 Gy over 17 d for those 12 months or older, and 10.5 Gy in 7 fractions of 1.5 Gy over 9 d in the case of infants. Dose volume histograms should be performed for liver and the remaining kidney to ensure that the doses to these organs at risk are kept within tolerance levels. At least two thirds of the remaining kidney should not receive a dose greater than 14.4 Gy, and at least half the liver should not receive a dose greater than 19.8 Gy.

Whole-abdominal and pelvic irradiation

For whole-abdominal and pelvic radiotherapy, the CTV will be the entire peritoneal cavity that extends from the dome of the diaphragm superiorly to the pelvic diaphragm inferiorly and laterally from the right to the left lateral abdominal wall. The superior border of the whole-abdominal and pelvic field will be placed approximately 1 cm above the dome of the diaphragm. The inferior border of the field will be placed at the bottom of the obturator foramen. The lateral borders of the field will be placed approximately 1 cm beyond the lateral abdominal wall. The femoral heads should be shielded during radiotherapy. An AP-PA is recommended for whole-abdominal and pelvic irradiation. The dose/fractionation schedule for whole-abdominal and pelvic radiotherapy is 19.5 Gy in 13 fractions of 1.5 Gy over 17 d for those 12 months or older. For these patients, the remaining kidney should be shielded to limit the dose to 14.4 Gy. In the case of infants, the whole-abdominal and pelvic dose is 10.5 Gy in 7 fractions of 1.5 Gy over 9 d. This treatment should be CT planned to allow dose volume histograms to be generated for organs at risk. This is especially important if a second phase of treatment to boost the dose to macroscopic residual disease is being contemplated (Section 9.1.8).

Boost for gross residual disease

Patients with gross residual disease after surgery may receive a second phase of treatment after flank or whole-abdominal and pelvic radiotherapy. This requires individualised consideration. Depending on factors such as the volume which would require treatment, and the age of the patient, a lower dose may be deemed safer, or the boost may be omitted. The GTV will be defined on the post-operative planning CT scan used for planning the first phase of treatment. The CTV will usually be the same as the GTV, but may be extended to ensure uniform irradiation of vertebral bodies. The PTV will be the CTV + 1 cm unless departmental quality control data indicate that a different margin is appropriate. The organs at risk will already have been delineated on the planning CT scan. Fields will be shaped with multileaf collimator (MLC) or customised blocks to conform to the PTV. The most appropriate field arrangement will be selected by the clinician taking into account the composite dose volume histograms for phase I and phase II combined, with respect to coverage of the PTV and the dose constraints to organs at risk as stated in Section 9.1.6. The dose will usually be 10.8 Gy in six fractions of 1.8 Gy over 8 d, but 10.5 Gy in seven fractions over 9 d may be more appropriate in infants or if the volume is large.

Whole-lung irradiation

Both lungs are irradiated regardless of the number and location of the metastases. Treatment should be CT planned with patient lying supine with the arms to the side, slightly away from the body. The CTV includes the entire lungs, mediastinum and the pleural recesses. The CTV to PTV margin should take account of respiratory movement and is likely to be about 1 cm superiorly and laterally and 2 cm inferiorly. AP-PA and posterior parallel-opposed field will be used such that the PTV is encompassed with the 95% isodose. CT planning will take into account and correct the increased transmission through lung tissue. The inferior border of the field should lie in an intervertebral space, often below L1. The shoulder joints should be protected by MLC or cerrobend shielding. The whole-lung irradiation (WLI) dose/fractionation schedule for those aged 12 months or over is 15 Gy with lung correction in 10 fractions of 1.5 Gy over 12–14 d. For infants, it is 10.5 Gy in seven fractions of 1.5 Gy over 9 d. If patients require both whole-lung and infra-diaphragmatic irradiation, then both fields should be treated simultaneously whenever possible. As the volumes for WLI often abut or overlap with the volumes for flank or whole-abdominal and pelvic radiotherapy, the contiguous areas should be treated in

the first instance as a single volume with a single pair of appropriately shaped AP-PA and posterior parallel-opposed fields. For such a large volume, a fraction size of 1.5 Gy will be used. The fields will be reduced in size (off the lungs) after 10 fractions (15 Gy) to cover only the infra diaphragmatic volume. If the WLI volume and the flank volume appear well separated, they may be treated simultaneously as two separate areas, but great care must be taken when planning to ensure an adequate gap so that there is no overlap. Similarly, if WLI and infra-diaphragmatic radiotherapy are given at different times, care must be taken to ensure that there is no overlap.

Localized foci of lung disease persisting 2 weeks after the delivery of WLI may either be excised or given an additional 7.5 Gy in five fractions. The volume of the lungs included in this boost irradiation field should be <30% in order to limit the acute and long-term pulmonary complications that could result from higher doses of irradiation.

Liver irradiation

The entire liver is included in the irradiation portal only if the liver is diffusely involved (19.8 Gy in 11 fractions of 1.8 Gy.) In infants the dose/fractionation schedule should be 15 Gy in 10 fractions of 1.5 Gy. If the entire liver volume is not involved, then only the metastases with a margin of 2 cm is irradiated. Additional boost irradiation doses of 5.4 to 10.8 Gy may be administered to limited volumes (<75% of the entire liver) at the discretion of the clinical oncologist. While irradiating the liver, the dose to the upper pole of the remaining kidney should be monitored. A posterior kidney block may be inserted in order to limit the remaining kidney to ≤14.4 Gy. An AP-PA technique is recommended for liver irradiation.

Brain irradiation

In patients with brain metastases, the whole brain is included in the irradiation field to a dose of 21.6 Gy in 12 fractions of 1.8 Gy. A boost of at least 10.8 Gy is required to site of metastases. In patients with ≤3 circumscribed lesions especially in patients younger than 3 years, a limited volume (tumour or tumour bed only with 0–1 cm margin) boost dose of 10.8 Gy in 6 fractions using intensity-modulated radiation therapy (IMRT) or sterotactic radiotherapy may be administered after whole-brain irradiation to 21.6 Gy.

A lateral parallel-opposed technique (right and left lateral) is recommended for whole-brain irradiation.

Bone irradiation

In patients with bone metastases, the GTV is the lesion as shown on appropriate imaging, which may include skeletal scintiography, plain radiographs MRI and CT. The clinical target volume will usually include a margin of apparently healthy bone up to 2 cm. A narrower margin may be appropriate where the metastasis is close to the edge of the bone. Irradiation of the epiphyses should be avoided where possible to diminish late effects. An appropriate margin should be added for the PTV, taking into account the technique of immobilisation used. The entire bone need not be irradiated. An AP-PA technique is usually recommended for bone irradiation, depending on the anatomical site. The bone irradiation dose is 25.2 Gy in 14 fractions of 1.8 Gy, but may be modified if appropriate.

Lymph node irradiation

Lymph nodes with metastatic tumour that have not been surgically removed should receive radiation therapy. Groups of lymph nodes which were involved at presentation should be irradiated in their entirety. The GTV will be the nodal area including any residual mass after chemotherapy as defined on the planning CT scan. The CTV will usually be a 1 cm margin around the GTV. The margin for PTV definition will depend on immobilisation and individual departmental data. If vertebrae are to be irradiated, the whole vertebral body shall be included in the fields. For mediastinal and abdominal nodes, a parallel-opposed field arrangement usually gives best coverage of the PTV. Where possible, nodal areas will be treated in continuity with the primary tumour site or other metastatic sites requiring irradiation. The dose will usually be 19.8 Gy in 11 fractions of 1.8 Gy.

Target dose

The daily dose to ICRU prescription points shall be 1.8 Gy, except in younger children (e.g. <3 years) or when large volumes (e.g. whole lung or whole abdomen and pelvis) are to be treated.

Extrarenal 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.

Extrarenal non-CNS rhabdoid tumours

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

These total doses and fractionation schedules may need to be modified taking into account factors including the age of the child, the volume requiring irradiation, critical normal structures and co-morbidity.

Equipment

Treatment will usually be with x-ray photons of 4–20 MV from a linear accelerator. The use of cobalt teletherapy is not acceptable.

In some circumstances, the use of electrons may result in a more favourable dose distribution.

Similarly, interstitial or intacavitary brachytherapy may be preferable in certain circumstances, such as with tumours at gynaecological, extremity and some non-parameningeal head and neck primary sites. Brachytherapy should not be used without careful discussion and is only appropriate in specialised treatment centres.

Proton therapy is permitted in this study in specialised treatment centres.

Protocol target volumes

Three-dimensional treatment planning is strongly encouraged for patients treated on this study.

All treatment planning, regardless of whether it is standard or three-dimensional conformal/IMRT, will be based upon the following target definitions. Treatment will be prescribed to the PTV, which will be derived from the GTV and CTV as follows:

GTV

The GTV is defined as the pre-treatment visible and/or palpable disease defined by physical examination, operative surgical findings, computer tomography, or magnetic resonance imaging. The T_1 MR image with contrast is usually optimal imaging study. In special circumstances, changes can be made in this definition based upon the post-operative geometry of the target volume. In patients who have undergone primary surgical tumour resection, the entire surgical scar should be included in the GTV. However, in general, the GTV does not change based on any surgical resection or chemotherapy response.

CTV

For all Clinical Groups, the CTV is defined as the GTV + 1.5 cm (but not extending outside of the patient). For some sites, the definition of the CTV is modified to account for specific anatomic barriers to tumour spread. The CTV will always include the entire draining lymph nodes chain if the regional nodes are clinically or pathologically involved with tumour. Patients with gross residual disease and primary sites in the head and neck and vulva/uterus who do not undergo second look operations may have second CTV and PTV defined for a cone down boost. The patients will receive a total dose of 50.4 Gy given to the PTV.

PTV

For all Clinical Groups, the PTV is defined as the CTV plus an institution specific margin to account for day-to-day setup variation related to the ability to immobilise the patient and physiological motion of the CTV.

Planning organ-at-risk volume

Planning organ-at-risk volumes (PRV) will be defined for each organ at risk defined in Section 14, Radiotherapy Guidelines, and for any other organ that the treating clinical oncologist wishes to limit to a specific dose. The PRV is defined as the volume of the organ at risk plus a margin to account for that organ's positional uncertainty.

Special modifications of GTV and CTV for certain sites

➢*Orbit:*. For orbit primaries, the CTV will not extend outside the bony orbit, providing there is no bone erosion of the orbit.

➢*Thorax:*. Tumours which have displaced a significant amount of lung parenchyma which has subsequently returned to normal anatomic position following surgical debulking will have the GTV defined as the pre-operative tumour volume excluding the intra-thoracic tumour which was debulked. However, all areas of pre-operative involvement of the pleura will be included in the GTV.

➢*Bladder/prostate, perineum, pelvis, biliary tree and abdomen:*. Tumours which have displaced a significant amount of bowel which has subsequently returned to normal anatomic position following surgical debulking will have the GTV defined as the pre-operative tumour volume excluding the intra-abdominal or intra-pelvic tumour which was debulked. However, all areas of pre-operative involvement of the peritoneum or mesentery, and the site of origin, will be included in the GTV.

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.

Prescribed dose and fractionation

The total radiotherapy dose for the various clinical groups are indicated in the table below:

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

All radiation should be given at 1.8 Gy per fraction with one fraction given per day. Five fractions should be given per week.

Interruptions

Patients requiring an interruption in radiotherapy (i.e. for low counts, infection, toxicity) will receive a modification in the schedule as shown in the tables below

Patients prescribed 36 Gy (Gp I)

Timing	Fx size (Gy)	# Fx	Total Dose (Gy)	Total time
Normal and/or up to 2-week split	1.8	20	36	4–6 Weeks
2- to 3-week split	1.8	21	37.8	6–7 Weeks
>3-week split	1.8	22	39.6	>7 Weeks

Patients prescribed 45.00 Gy (Gp II)

Timing	Fx size (Gy)	# Fx	Total dose (Gy)	Total time
Normal and/or up to 2-week split	1.8	25	45	5–7 Weeks
2- to 3-week split	1.8	26	46.8	7–8.4 Weeks
>3-week split	1.8	27	48.6	>8.4 Weeks

Patients prescribed 50.40 Gy (Gp III)

Timing	Fx size (Gy)	# Fx	Total dose (Gy)	Total time
Normal and/or up to 2-week split	1.8	28	50.4	5.4–7.3 Weeks
2- to 3-week split	1.8	29	52.2	7.4–8.4 Weeks
>3-week split	1.8	30	54.0	>8.4 Weeks

Normal tissue sparing

It is important to protect normal vital structures whenever possible. Such shielding must be weighed against the possibility of under treatment of known tumour-bearing tissue.

The recommended upper dose limits for different organs are shown in the table below. These limits are the same as, or less than, those used in the previous IRS studies and have not been associated with excessive toxicity when used with chemotherapy.

Normal tissue tolerance

Organ	Dose limit (Gy)
Optic nerve and chiasm	50
Lacrimal gland	41.4
Small bowel	45.0
Spinal cord	45.0
Lung (when >$^1/_3$ but <$^1/_2$ of total lung volume is in the PTV)	18.0
Lung (when >$^1/_2$ of total lung volume is in the PTV)	15.0
Whole kidney	19.8
Whole liver[a]	23.4

[a] Tolerance for partial liver radiation: when two third of the liver volume is included in the initial radiation port and more than one third of the liver requires a boost beyond the maximum whole liver dose (23.4), the total dose to the boost volume may be limited to a maximum of 30 Gy. The boost volume should not exceed two third of the total liver volume.

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