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Original Paper

Treatment of Non-metastatic Rhabdomyosarcomas in Childhood and Adolescence. Results of the Second Study of the International Society of Paediatric Oncology: MMT84

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The second International Society of Paediatric Oncology (SIOP) study for rhabdomyosarcoma (MMT84) had several goals. The two principal aims were: (1) to improve the survival of children with rhabdomyosarcoma; and (2) to reduce the late effects from therapy by restricting the indications for surgery and/or radiotherapy after good response to initial chemotherapy. A further aim was to investigate the role of high-dose chemotherapy in young patients with parameningeal primary tumours. 186 previously untreated eligible patients entered the study. Patients with completely resected primary tumour received three courses of IVA (ifosfamide, vincristine and actinomycin D). Patients with incompletely resected tumour received six to 10 courses of IVA according to stage. Patients achieving complete remission with chemotherapy alone did not usually receive radiotherapy or undergo extensive surgery, but patients remaining in partial remission received local therapy with surgery and/or radiotherapy. Only patients over 5 years of age with parameningeal disease and patients over 12 years with tumours at any site were given systematic irradiation. Complete remission was achieved in 91% (170/186) of all patients. With a median follow-up of 8 years, the 5-year overall survival was 68% (± 3% standard error of the mean (SEM)) and the 5-year event-free survival 53% (± 4% SEM). These results show an improvement over previous SIOP study (RMS75) in which survival was 52% and event-free survival was 47%. Among the 54 patients who exhibited isolated local relapse, 35% (19/54) survived in further remission longer than 2 years after retreatment, including local therapy (surgery ± radiotherapy). Analysis of the overall burden of therapy received by all surviving children (including primary treatment and treatment for relapse if required) showed that 24% (28/116) were treated by limited surgery followed by three courses of IVA, 29% (34/116) were treated by chemotherapy alone (after initial biopsy) and 13% (15/116) received chemotherapy plus conservative local treatment (limited surgery or radiotherapy for residual disease). Only 34% (39/116) received intensive local therapy defined as radical wide field radiotherapy or radical surgery or both. Compared with the results obtained in the previous SIOP study, treatment in MMT84 was based on response to initial chemotherapy and, despite an overall reduction of the use of local therapy, significantly improved survival for patients with non-metastatic disease. This trial, also for the first time, provides evidence that retreatment after local relapse can achieve long-term second remissions. © **1998 Elsevier Science Ltd. All rights reserved.**

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INTRODUCTION

RHABDOMYOSARCOMA ACCOUNTS for 4–8% of cancers in children under the age of 15 years [1]. Dramatic improvement in survival has been observed since 1970 following the introduction of multimodal therapy strategies [2, 3]. However, with an increasing number of survivors and longer follow-up, important late sequelae of treatment have been identified, particularly bone and soft tissue growth impairment, cosmetic sequelae and neuropsychological damage from radiotherapy; male sterility from alkylating agents; and cardiac failure after anthracycline treatment [4–6].

In the first International Society of Paediatric Oncology (SIOP) rhabdomyosarcoma study (RMS75), 281 children were treated between 1975 and 1983 with an overall survival (OS) of 52% and an event-free survival (EFS) of 47% [7]. In that study, chemotherapy was given for 18 months utilising an alternating VAC–VAD schedule (VAC: vincristine, actinomycin D and cyclophosphamide; VAD: vincristine plus doxorubicin). In 1978, the duration of chemotherapy was reduced to 8 months for patients with complete resection of the tumour at diagnosis. Patients with incomplete initial surgical resection, including those with only biopsy at diagnosis, were included in a randomised trial designed to compare the efficacy of early local therapy (after one course of chemotherapy) with late local therapy, after a maximum reduction of the tumour size with a longer course of chemotherapy. Three-year OS was 40% for this group of patients and the two treatment strategies yielded equivalent results in terms of: (a) initial local control; (b) local recurrence; or (c) subsequent risk of metastases. However, patients receiving late local therapy directed to the residual disease achieved the same OS and, presumably, less severe sequelae [8].

The rationale for the MMT84 study was based upon the results of RMS75 and on preliminary data on the efficacy of ifosfamide which, by the end of the RMS75 study, had been identified as an effective agent for rhabdomyosarcoma [9], adult soft tissue sarcoma [10] and possibly cyclophosphamide-resistant tumours [11]. The five primary objectives of MMT84 were: (i) to determine whether the IVA combination (ifosfamide, vincristine, actinomycin D) improved outcome compared with RMS75 which included cyclophosphamide (OS 52% at 5 years in RMS75); (ii) to maintain survival for patients with localised completely resected tumours whilst further reducing the intensity of treatment by omitting doxorubicin and reducing the overall treatment duration to 3 months (as compared with 8 months in RMS75); (iii) to evaluate whether local treatment for patients with incompletely resected disease could be safely based on their response to the initial chemotherapy, without compromising overall survival. It was intended that patients with complete remission at week 30 should receive no additional local therapy; (iv) to determine whether local relapse in patients previously treated by chemotherapy alone without definitive local therapy could be salvaged by the use of further chemotherapy and local treatment (surgery and/or radiotherapy); and finally (v) to investigate the value of high-dose chemotherapy in improving the outcome of patients with high-risk parameningeal tumours.

PATIENTS AND METHODS

Study design

The study enrolled patients aged 3 months to 18 years who had received no previous treatment, except surgery. There was no restriction regarding the interval between the date of initial biopsy or surgery and inclusion in the study.

All patients with malignant mesenchymal tumours were eligible for inclusion in the study, but this report details only the outcome for patients with confirmed rhabdomyosarcoma (excluding those with extra-osseous Ewing's sarcoma and undifferentiated sarcomas).

Staging

The extent of disease was determined by clinical examination, standard X-rays and computed tomography (CT) scan or magnetic resonance imaging (MRI). Ultrasound examination was performed in evaluating intra-abdominal or pelvic tumour sites. Examination under general anaesthesia was performed in the case of vaginal tumours. Particular attention was paid to the status of regional lymph node involvement. Cytological examination or biopsy was undertaken for any clinically suspicious or obviously enlarged lymph nodes in the region of the primary tumour. Abdominal and pelvic CT scans were advocated for all lower limb tumours. Abdominal CT and ultrasound examination of the para aortic area were recommended for paratesticular tumours. Cerebrospinal fluid examination was required for all head and neck tumours.

Chest X-ray and technetium bone scan, with plain X-rays of abnormal sites, were required for the detection of distant metastases. A bone marrow aspirate was performed in all cases and two bone marrow trephine biopsies were requested in cases where metastatic disease was identified at another site.

Open surgical biopsy was normally performed, except in an emergency when urgent diagnosis could be established on the basis of a needle biopsy.

Table 1. *Pretreatment and postsurgical TNM clinical staging system for childhood rhabdomyosarcoma*

Pretreatment staging		
Stage I		
	T1	Tumour localised in the organ or tissue of origin
	N0	No evidence of regional lymph node involvement
	M0	No evidence of metastasis
Stage II		
	T2	Tumour involving one or more contiguous organ or tissue or with adjacent malignant effusion
	N0	
	M0	
Stage III		
	Any T	
	N1	Evidence of regional lymph node involvement
	M0	
Stage IV		
	Any T	
	Any N	
	M1	Evidence of distant metastases
Postsurgical staging		
pT1		Tumour limited to organ or tissue of origin; excision complete and margins histologically free
pT2		Tumour invasion beyond the organ or tissue of origin; excision complete and margins histologically free
pT3		Tumour incompletely resected
	pT3a	Evidence of microscopic residual tumour
	pT3b	Evidence of macroscopic residual tumour or biopsy alone
	pT3c	Adjacent malignant effusion

All tumours were reviewed by an international panel of pathologists and classified according to the new international classification as botryoid, leiomyomatoid, embryonal or alveolar [12]. Clinical staging was based on the SIOP-UICC TNM classification which was agreed upon by an international workshop as best defining the pretreatment extent of the disease [13]. This system is detailed in Table 1.

Tumour sites, defined according to the coding system for childhood tumours [14], were allocated into six subgroups as follows: (i) non-parameningeal orbit; (ii) parameningeal head and neck (including orbit with parameningeal extension); (iii) non-parameningeal head and neck; (iv) genitourinary (distinguishing between bladder/prostate and non-bladder/prostate sites—paratesticular, vulva, vaginal and uterine sites); (v) limbs; and (vi) 'others'. The definition of parameningeal sites was that agreed internationally and included tumours arising in, or extending into the middle ear, nasopharynx, infratemporal fossa and paranasal sinuses. Two subgroups of parameningeal disease were recognised. Patients were considered to have a high risk of meningeal extension if there was any erosion of the base of the skull, cranial nerve palsies or intracranial tumour extension. Those without any of these characteristics were considered to have a low risk of meningeal extension.

Treatment schedule

The overall schema for the treatment schedules used are shown in Figure 1 and the allocation between treatment schedules (defined by site, stage and age) is detailed in Table 2. IVA courses consisted of ifosfamide 3 g/m^2 days 1 and 2, actinomycin D 1.5 mg/m^2, day 1, vincristine 1.5 mg/m^2, day 1. Drug doses were reduced for infants younger than 1 year to avoid excessive toxicity: an initial reduction of 50% was used for children younger than 6 months and of 33% for those aged between 6 and 12 months.

Group 84.1. Patients with a completely excised stage I tumour (stage I pT1 or pT2) received three courses of IVA and no radiotherapy.

Group 84.2. Patients with a completely excised stage II tumour (stage II pT2) and those with any stage I or stage II tumour with microscopic residual disease after initial surgery (stage I–II pT3a) received three courses of IVA then underwent

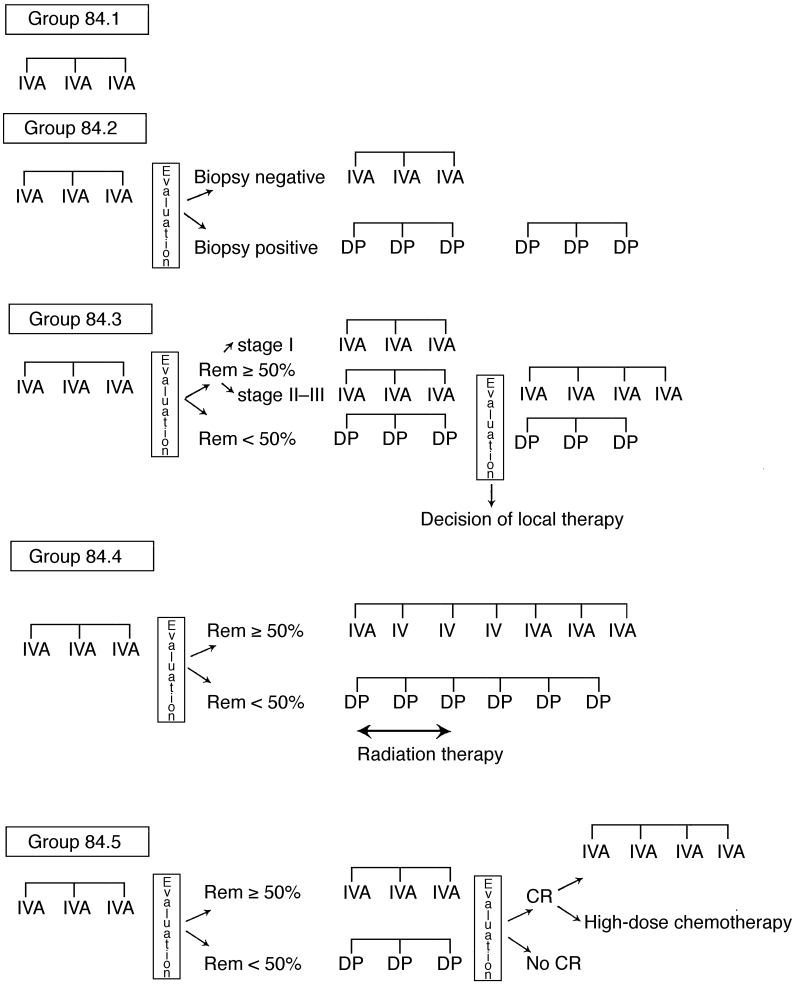

Figure 1. Treatment schedules in the MMT84 study. Group 84.1, completely excised stage I tumours (stage I pT1 or I pT2) ($n = 27$); group 84.2, completely excised stage II tumours (stage II pT2) and any tumour with microscopic residual disease after initial surgery (stage I–II pT3a) ($n = 35$); group 84.3, macroscopic residual disease after initial surgery (stage I or II pT3b, c—except high-risk parameningeal tumour) and node positive stage III tumours regardless of surgery ($n = 92$); group 84.4, high-risk parameningeal tumour in patients aged 5 years or older ($n = 18$); group 84.5; high-risk parameningeal tumour in patients younger than 5 years old ($n = 14$). IVA = ifosfamide (3 g/m^2 day 1 and 2), vincristine (1.5 mg/m^2 day 1, maximum dose 2 mg), actinomycin D (1.5 mg/m^2 day 1, maximum dose 2 mg); DP, doxorubicin (60 mg/m^2 day 1), cisplatin (100 mg/m^2 day 1); rem, remission.

Table 2. Number of patients in each treatment group according to clinical TNM stage and site of the primary

	Surgical stage (all sites except parameningeal)				Low-risk parameningeal	High-risk parameningeal	
Clinical stage	pT1	pT2	pT3a	pT3b,c		>5 years	≤5 years
Stage I ($n=57$)	22 (84.1)	5 (84.1)	14 (84.2)	16 (84.3)	0 (84.3)	0 (84.4)	0 (84.5)
Stage II ($n=105$)	–	6 (84.2)	15 (84.2)	55 (84.3)	8 (84.3)	12 (84.4)	9 (84.5)
Stage III ($n=24$)	0 (84.3)	1 (84.3)	2 (84.3)	9 (84.3)	1 (84.3)	6 (84.4)	5 (84.5)

The treatment schedule is indicated in parenthesis for each subgroup. Details of treatments 84.1–84.5 are shown in Figure 1.

a second look operation, whenever possible. Patients with surgically/histologically confirmed complete response were given three additional courses of IVA without radiation therapy. Patients who had a positive biopsy were given second-line chemotherapy with doxorubicin (60 mg/m^2 day 1) plus cisplatin (100 mg/m^2 day 1) (DP), without local therapy, except patients over 12 years of age who then received systematic radiotherapy.

Group 84.3. Patients with macroscopic residual disease after initial surgery (stage I or stage II pT3b or c—except high-risk parameningeal tumour) and all those with stage III disease were given initial IVA chemotherapy. A first evaluation was performed after two courses and IVA was continued only if patients achieved at least 25% tumour response. Non-responding patients were given the second-line chemotherapy combination consisting of DP. In responding patients, a second evaluation was performed after the third IVA course and IVA was continued only in patients who had achieved at least a partial response ($\geq$50% reduction in tumour mass). Patients who failed to achieve a partial response after IVA×3 (poor responders) were changed to second-line treatment (DP). Local therapy was given to residual tumour in patients with measurable remaining mass after six courses of chemotherapy (IVA or IVA followed by DP). Complete clinical remission was assessed pathologically (by resection of a residual mass or multiple biopsies of tumour bed) as often as possible. Patients who achieved remission after chemotherapy alone received a total of six courses of treatment if they had stage I disease or a total of 10 courses of treatment if they had stage II or stage III disease. The maximum cumulative exposure to ifosfamide was 60 g/m^2, and to doxorubicin was 360 mg/m^2.

Group 84.4. Patients aged $\geq$5 years with high-risk parameningeal rhabdomyosarcoma received local radiation therapy after the third course of IVA (or after two courses of IVA and two courses of DP in case of a poor response to initial IVA courses). The prescribed dose of radiation was 45 Gy to the tumour volume with particular attention to margins. When the tumour extended intracranially, 30 Gy was given to the whole cranium with a 'boost' of 15 Gy to the primary tumour. Ifosfamide and vincristine were continued during radiotherapy and a total of 10 courses of chemotherapy was given. No intrathecal chemotherapy was administrated.

Group 84.5. Patients aged <5 years with high-risk parameningeal tumour were not given radiotherapy if they achieved complete response after six courses of chemotherapy. The study was designed to include a randomised trial to compare the outcome of patients who received conventional chemotherapy (10 courses of IVA) with those allocated to receive consolidation therapy with high-dose melphalan and bone marrow transplantation support.

Statistical methods

Analyses were first performed on the whole cohort and then according to different criteria: quality of surgery, pre-treatment TNM stages, pathological subtype and sites, using the 'intention to treat' principle. Thus, all eligible patients, regardless of compliance to the protocol, were included in the analysis.

Complete remission was defined as either the absence of any residual radiological abnormalities, assessed pathologically if possible, or the presence of residual abnormalities which remained stable for 6 months after the end of therapy.

The starting point for survival analysis was the date of the start of primary treatment. Prognosis was defined both by the duration of survival and of EFS. For EFS, events were defined as relapse after complete remission or death from any cause (including progression of disease without achievement of complete remission, or toxicity). If a patient failed to achieve complete remission, the time point for failure was the date of death as the date of progression was not registered. OS and EFS curves were calculated using the Kaplan–Meier method [15]. The statistical significance of each variable was first tested by the log-rank test (univariate procedure) [16]. Multivariate analysis was then performed using the Cox proportional hazard model (BMDP programme). Multivariate analysis models were determined by the likelihood ratio test. A stepwise procedure was used to identify the major prognostic events amongst clinical and pathological factors [17].

RESULTS

Patient population

Of 250 patients with rhabdomyosarcoma enrolled by 31 institutions, from January 1984 to December 1988, only 186 (74%) had adequate review of the diagnostic material by the Pathology Review Committee. In the other patients, no material was received or was too poor for confirmation of the diagnosis and only patients with satisfactory review were included in the analysis.

Patients' characteristics are shown in Table 3. There were more boys ($n=120$, 65%) than girls. The median age at diagnosis was 6 years and the mean age was 7 years. Seventy-eight per cent ($n=146$) of the patients were younger than 10 years at the time of diagnosis, 17% ($n=32$) were younger than 2 years, and 7.5% ($n=14$) were aged 1 year or less. Only 22% ($n=40$) were aged 12 years or more.

The Pathology Review Committee classified 19 tumours as botryoid or leiomyomatoid, 140 as embryonal and 27 as alveolar. Distribution of tumours according to site, stage, T status, size and mean age of the patients is shown in Table 4. Of the 41 patients with parameningeal tumours, 32 (78%) were at high risk of meningeal involvement. As shown in Table 3, patient characteristics in the RMS75 study and in MMT84 were similar, except for the stage distribution, with

Table 3. Comparison of the patients with no detectable metastases at diagnosis in RMS75 and MMT84

	RMS75 $n=281$ (%)	MMT84 $n=186$ (%)	P value
Sex			
Boys	174 (62)	120 (65)	
Girls	107 (38)	66 (35)	NS
Age			
< 2	54 (19)	31 (17)	
2–4	92 (33)	59 (32)	
5–9	95 (34)	56 (30)	NS
10 +	40 (14)	40 (21)	
Clinical stage			
I	115 (41)	57 (31)	
II	117 (42)	105 (56)	< 0.05
III	49 (17)	24 (13)	
Lymph node involvement			
Yes	49 (17)	24 (13)	
No	232 (83)	162 (87)	NS
Primary site			
Head and neck			
Orbit	30 (11)	19 (10)	
Non-parameningeal	46 (16)	17 (9)	
Parameningeal	59 (21)	41 (22)	
Genito-urinary			NS
Bladder/prostate	39 (14)	14 (8)	
Non-bladder/prostate	36 (13)	35 (19)	
Limbs	28 (10)	23 (12)	
Other	43 (15)	37 (20)	
Pathology			
Non-alveolar	230 (82)	159 (85)	
Alveolar	51 (18)	27 (15)	NS

NS, not significant.

a higher rate of stage II (56% versus 42%, respectively) and a lower rate of stage I (31% versus 41%, respectively) in the MMT84 study than in RMS75.

The median follow-up time of survivors was 470 weeks (9 years), ranging from 30 to 674 weeks. Ninety-two per cent (115/125) of surviving patients were followed for 5 years or more, with a median follow-up, after relapse, of 86 months (7.2 years). The median follow up overall was 8 years.

Complete remission

Complete remission was achieved in 91% (170/186) of patients, but the rate varied according to stage: 100% in patients with stage I pT1 or pT2 tumours, by definition; 100% in stage I pT3; 89% in stage II; and 83% in stage III. The time required to achieve complete remission ranged from 1 to 23 months (median 4 months). Twenty per cent (34/170) of the complete remissions were achieved after initial surgery (pT1, pT2); 45% (77/170) after incomplete surgery and chemotherapy, but without radiotherapy; 10% (17/170) after chemotherapy and surgery and/or radiotherapy for a minimal residual tumour; 6% (10/170) after chemotherapy with extensive surgery; and 19% (32/170) after chemotherapy and radiotherapy to the initial tumour volume. 23 of this last group of 32 patients received radiation therapy for failure to achieve a complete remission with induction chemotherapy and 9, all more than 5 years of age, received local radiation therapy for a high-risk parameningeal tumour. Overall, 59 of the 136 patients (43%) in whom surgery was initially incomplete (pT3) did not require additional surgery or radiotherapy to obtain a complete remission.

Overall treatment outcome

Five-year EFS (± standard error of the mean (SEM)) for the 186 patients was 53 ± 4% and OS was 68 ± 3% (Figure 2). OS was better than in the RMS75 study (68% versus 52%) despite a similar EFS (53% versus 47%) (Figure 2b). 16 patients (9%) died without achieving control of their tumour. Of the other 170 patients who achieved complete response, 97 (57%) were still in first complete remission at 5 years. 72 patients (42%) subsequently relapsed and 1 patient died from cardiotoxicity in first remission. Of those who relapsed, 23 are alive in remission after relapse (19 with more than 2 years of follow-up since the last relapse) and 49 died after relapse.

The clinical characteristics of the children ineligible for the study because of lack of pathology review and their survival rates (5-year OS and EFS, respectively, 62 ± 6% and 47 ± 6%) were similar to the patients who are analysed here (68 ± 3% and 53 ± 4%, respectively).

Prognosis by therapeutic groups (Table 5)

*Patients with completely resected localised disease (IpT1, IpT2) (*n = 27, *treatment group* 84.1*).* The 5-year EFS and OS rates were 85% (± 12) and 89% (± 12), respectively, compared with 63% (± 9) and 74% (± 8) for patients treated in the RMS75 study. It appears that three courses of IVA given over 2 months were as effective as 8 months of treatment with more intensive chemotherapy (4 VAC + 4 VAD).

*Patients with completely resected stage II (IIpT2) or with incomplete initial surgery (IpT3a,b,c; IIpT3a,b,c), or with stage III (*n = 159, *treatment groups* 84.2, 84.3, 84.4, 84.5*) (*i.e. *all localised stage patients except stage I completely resected).* The 5-year EFS and OS rates were 47% (± 4) and 65% (± 4), respectively, compared with 45% (± 3) and 50% (± 3) for

Table 4. MMT84 distribution according to site, clinical TNM stage, T status, size of the primary and age at diagnosis

	No. of patients (%)	TNM stage I	TNM stage II	TNM stage III	T1:T2	Size < 5 cm:> 5 cm	Mean age (months)
Orbit	19 (10)	9	10	—	9:10	15:3	64
Non-parameningeal head and neck	17 (9)	7	9	1	7:10	11:6	84
Parameningeal head and neck	41 (22)	—	29	12	0:41	9:26	82
Genito-urinary bladder/prostate	14 (8)	1	12	1	1:13	5:9	36
Non-bladder/prostate	35 (19)	22	11	2	24:11	22:11	65
Limbs	23 (12)	13	9	1	13:9	9:10	110
Other sites	37 (20)	5	25	7	5:31	7:28	76
Total	186	57 (31%)	105 (56%)	24 (13%)	59:125 (32%:68%)	78:93 (46%:54%)	

Table 5. Five-year event-free and overall survival in the different treatment groups

Treatment group	% 5-year event-free survival (± SEM)	% 5-year (± SEM) overall survival
84.1	85 (± 12)	89 (± 12)
84.2	66 (± 6)	83 (± 7)
84.3	42 (± 5)	61 (± 5)
84.4	50 (± 10)	62 (± 10)
84.5	36 (± 13)	50 (± 10)

SEM, standard error of the mean.

patients treated in the RMS75 study. In the MMT84 study, 89 (56%) of patients did not receive any local therapy after complete response to primary chemotherapy. In the RMS75 study, all patients with incompletely resected tumour received radiotherapy to the primary site. In the MMT84 study, duration of treatment depended upon initial response to chemotherapy, but was completed in a maximum of 36 weeks, whereas VAC–VAD chemotherapy was given over a 18 month period in the RMS75 study. Thus, the EFS and OS rates were improved in the MMT84 study, despite shorter chemotherapy and without radiation therapy.

Prognosis by clinical stage

Figure 3(a, b) and Table 6 show the outcome by clinical stage for all treatments combined. Patients with stage I tumours fared much better than those with more advanced disease, both in terms of EFS and OS. In terms of EFS, there was no significant difference between stage II and stage III tumours, but the OS rates were higher for stage II tumours because there were many durable second remissions.

Prognosis by pathological subtype

Histological subtype had a significant impact on both EFS and OS. Patients with alveolar tumours fared much worse than those with other histological findings. The 5-year EFS rates were 33% versus 56% ($P = 0.01$) for alveolar versus non-alveolar histology and OS rates were 44% versus 72% ($P = 0.02$), respectively (Figure 4).

Prognosis by primary site

Figure 5(a, b) and Table 6 show prognosis by primary sites for all treatments combined and show striking differences in survival ($P < 0.001$). Patients with the most favourable prognosis were those with tumours involving the orbit or genito-urinary non-bladder/prostate sites (5-year OS = 88%). Tumours arising in miscellaneous 'other' sites had the lowest

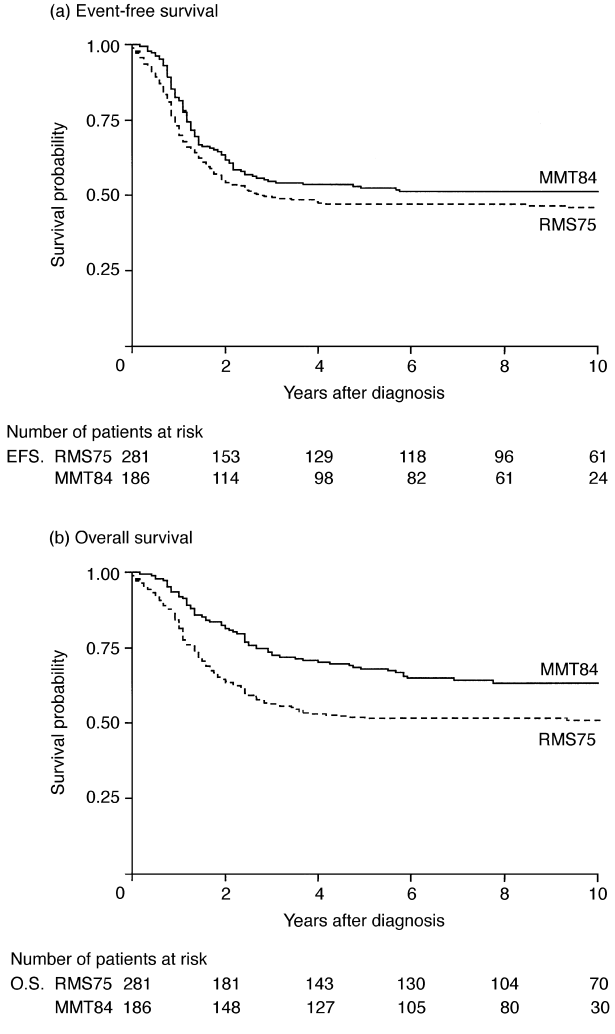

Figure 2. (a) Event-free survival (EFS) and (b) overall survival (OS) for all patients with localised tumour treated in MMT84 and in RMS75. RMS75, 5-year EFS = 47%, OS = 52%; MMT84, 5-year EFS = 53%, OS = 68%.

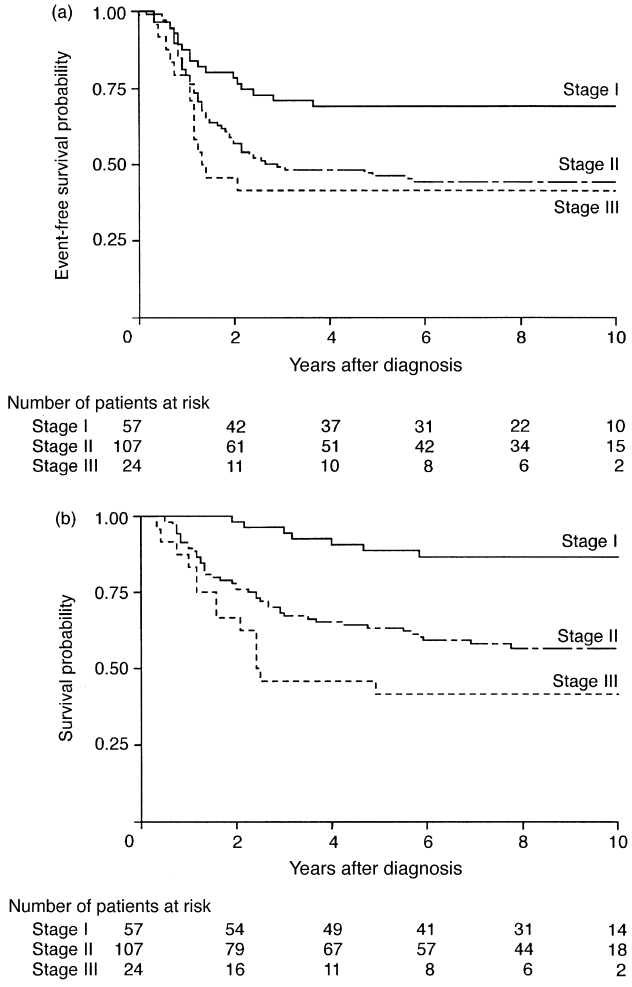

Figure 3. (a) Event-free survival (EFS) and (b) overall survival (OS) by clinical stage: 5-year EFS and OS, stage I 69% and 89%; stage II 47% and 63%; stage III 42% and 42%.

Table 6. Univariate analysis: 5-year event free survival (EFS) and overall survival (OS) by prognostic variables

Variables	*n*	% 5-year OS (SEM)	Relative risk of death*	Log-rank test *P*	% 5-year EFS (SEM)	Relative risk of event	Log-rank test *P*
Sex							
Boys	120	73 (4)	1	NS	55 (2)	1	NS
Girls	66	59 (6)	1.6		47 (6)	1.4	
Age (years)							
< 2	31	71 (8)	1	0.04	55 (9)	1	0.02
2–4	59	68 (6)	1.1		57 (7)	0.9	
5–9	56	78 (6)	0.7		60 (7)	0.7	
10 +	40	53 (8)	1.8		35 (8)	1.7	
T status							
T1	59	87 (5)	1	< 0.001	68 (6)	1	0.004
T2	125	60 (5)	3.6		45 (5)	2.1	
Unknown	2						
Tumour size (cm)							
≤ 5 cm	78	84 (4)	1	< 0.001	63 (5)	1	0.001
> 5 cm	93	54 (5)	2.8		41 (5)	2.0	
Unknown	15						
Clinical stage							
I	57	89 (4)	1	< 0.001	69 (6)	1	0.01
II	105	63 (5)	3.6		47 (5)	2.1	
III	24	42 (10)	6.1		42 (10)	2.5	
Lymph node involvement							
Yes	24	42 (10)	2.4	0.003	42 (10)	1.5	0.14
No	162	72 (4)	1		54 (4)	1	
Primary site							
Orbit	19	88 (8)	1	< 0.001	65 (12)	1	< 0.001
Non-parameningeal	17	77 (10)	3.3		35 (12)	2.4	
Parameningeal	41	58 (8)	5.6		42 (8)	2.1	
Genito-urinary bladder/prostate	14	79 (11)	2.2		64 (13)	1.2	
Genito-urinary non-bladder/prostate	35	88 (6)	1.1		85 (6)	0.4	
Limbs	23	65 (10)	4.1		48 (10)	2.1	
Other	37	45 (8)	7.2		35 (8)	3.0	
Pathology							
Non-alveolar	159	72 (4)	1	0.002	56 (4)	1	0.01
Alveolar	27	44 (10)	2.4		33 (9)	2.0	
Total	186	68 (4)			53 (4)		

*Relative risk of death (or event) is the ratio of observed deaths (or events) to expected deaths (or events). SEM, standard error of the mean; NS, not significant.

OS (5-year OS = 45%). Other tumours had an intermediate outcome, with 5-year OS ranging from 58 to 79%.

Amongst patients with parameningeal tumours, 32 were defined as high risk. The 18 patients with high-risk tumours above the age of 5 years were scheduled to receive irradiation to the primary tumour. In fact, 4 patients were not irradiated and 3 of these children relapsed locally. The 5-year EFS and OS of these patients were 50% (± 10) and 61% (± 10), respectively. 14 patients were less than 5 years of age and of these, 10 were given chemotherapy alone (with additional high-dose chemotherapy in 2 cases) and 4 were given radiation therapy because they did not achieve complete remission with chemotherapy alone. The planned randomised study was abandoned because of poor compliance (mainly due to the lack of a bone marrow transplant unit or reluctance by the treating physicians). The 5-year EFS and OS were 36% (± 13) and 50% (± 13). The small number of patients and the heterogeneity of local treatments within each group does not allow comparison between patients aged more or less than 5 years. However, among the group of 14 patients who were treated without radiation therapy, 10 relapsed locally, 5/10 with a contiguous meningeal extension. 5 of them were less than 4 years old at diagnosis. Only 2 of those 10 patients are in second continuous remission. However, among the 18 children treated with radiation therapy, initial local control of the disease was never achieved in 2 cases, 4 developed local relapses, 1 associated with diffuse meningeal involvement and 2 with metastases. 2 other children developed metastases without evidence of local relapse.

In the RMS75 study, all patients with parameningeal tumours, irrespective of age, were given radiation therapy with EFS and OS rates of only 24% and 25%, respectively [4]. The results in the MMT84 study represent an improvement, but it is likely that this relates not only to chemotherapy but also to better imaging of the tumour and to enlargement of the definition of the 'parameningeal sites' agreed between the eras of the two studies.

Differences between EFS and OS for different tumour sites are shown in Figure 5 and Table 6. This is mainly accounted for by the effect of previous radiotherapy on the possibility of successful retreatment of patients who relapse. Survival after relapse was most likely where patients had not already received radiotherapy and this mainly explains why the largest discrepancies between EFS and OS were for children with orbital, extremity and head and neck non-parameningeal tumours.

Prognosis study using Cox regression analysis

There were 184 patients for whom all clinical characteristics and outcome could be evaluated using the multivariate analysis. As shown in Table 6, univariate analysis showed that age, T status, tumour size, lymph node involvement, primary site ($P < 0.001$) and pathology ($P = 0.002$) were statistically related to OS. Only lymph node involvement was not related to EFS ($P = 0.14$). Using Cox regression, three of these six factors (T stage, histology and primary site) were selected by the stepwise procedure. The very similar relative risk of specific sites led us to consider the grouping of sites in four categories (orbit, genito-urinary, head and neck-limbs, 'other' sites).

The most important factors in predicting survival, in decreasing order, were T status, primary site and histology (Table 7). Clinical stage and tumour size were not selected in the Cox model because both are strongly dependent on T status.

Relapses: patterns and outcome

The median time between diagnosis and first relapse was 14 months (range 2–69 months). The majority of relapses (78%) occurred within 2 years of diagnosis. The 'first event' in the 72 patients who relapsed after complete remission was as follows: 11 (15%) developed isolated metastases and 61 (85%) developed a local relapse (7 with distant metastases). Of the 54 isolated local relapses, 47 (87%) occurred at the site of the primary, 3 (6%) in loco-regional lymph nodes, and 4 (7%) both at the site of the primary and in the nodes.

Patients with stage II and stage III disease had a similar overall relapse rate, higher than for those with stage I disease. Isolated local relapses were much more frequent than metastases in stage I and stage II disease, whereas metastases were as frequent as isolated local relapses in stage III disease.

Alveolar histology was associated with a significantly higher risk of relapse than non-alveolar tumours ($P = 0.01$), and with a significant higher risk of developing metastases (6/27 versus 12/159, $P = 0.02$).

Table 8 shows the type of relapse and outcome in relation to the type of initial treatment. Most of the patients who relapsed were those treated by chemotherapy alone after incomplete surgery ($n = 76$). Exactly half of these children ($n = 38$) relapsed locally, 2 developed simultaneous local

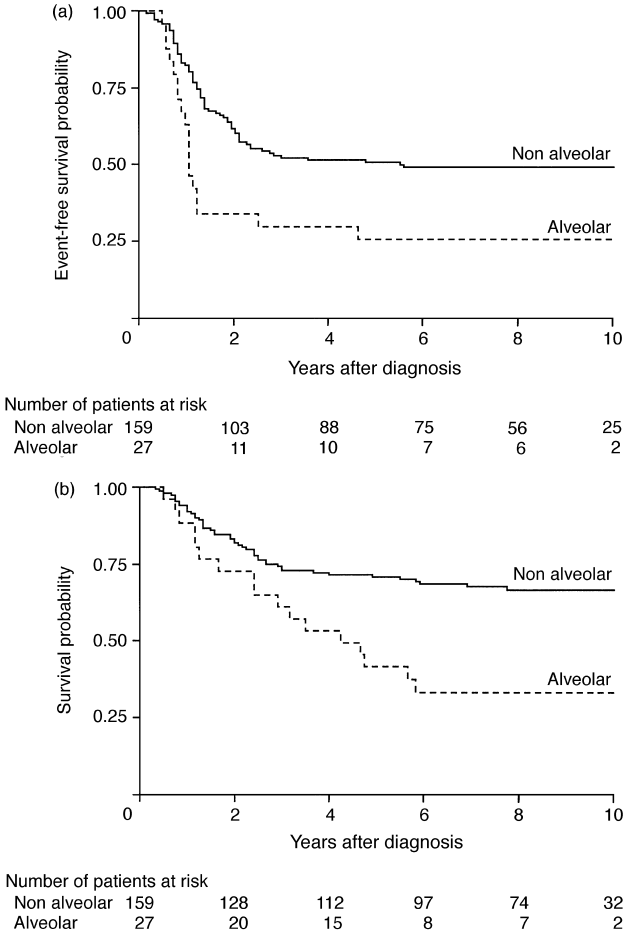

Figure 4. (a) Event-free survival (EFS) and (b) overall survival (OS) by histology: 5-year EFS and OS, non-alveolar tumour 56% and 72%; alveolar tumour 34% and 44%.

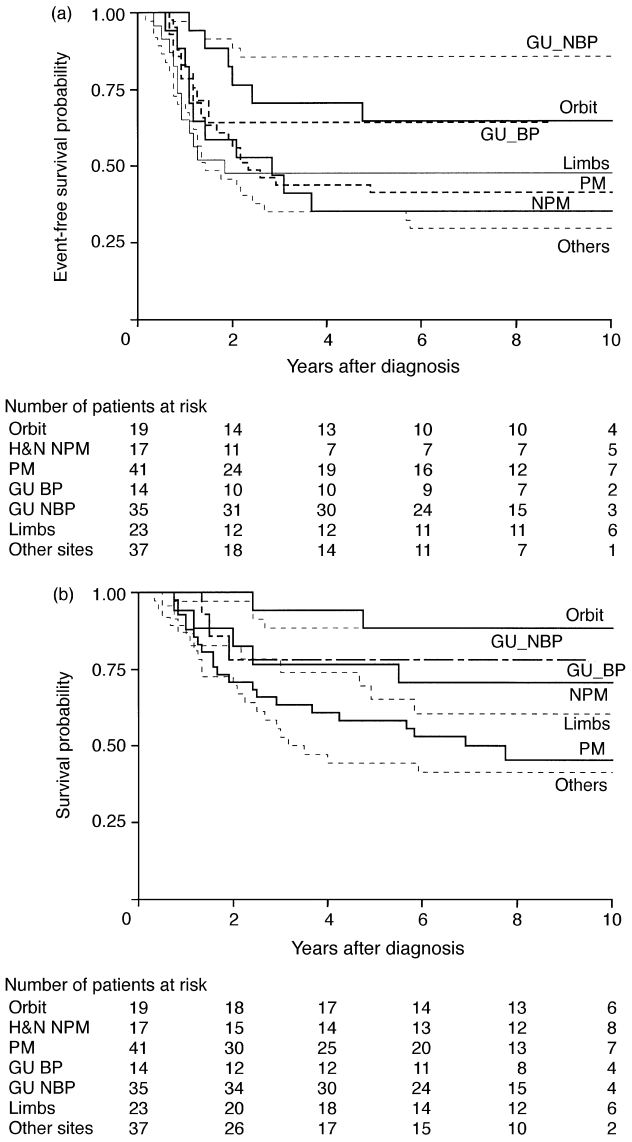

Figure 5. (a) Event-free survival (EFS) and (b) overall survival (OS) by site: 5-year EFS and OS, Orbit 65% and 88%; non-parameningeal head and neck (NPM) 35% and 77%; parameningeal head and neck (PM) 42% and 58%; genito-urinary bladder/prostate (GU-BP) 64% and 79%; genito-urinary non-bladder/prostate (GU-NBP) 85% and 88%; limbs 48% and 65%; other sites 35% and 45%.

Table 7. Cox regression model for patients with localised rhabdomyosarcoma for overall survival

Prognostic variables	Relative risk for each site	Relative risk after site grouping
T status	($P < 0.001$)	($P < 0.001$)
T1	1	1
T2	3.2	3.2
Site	($P < 0.03$)	($P < 0.01$)
Orbit	1	1
Bladder/prostate	1.9	1.9
Paratesticular, vagina	1.8	
Head and neck non-parameningeal	4.4	
Head and neck parameningeal	4.6	4.6
Limbs	4.7	
Other sites	6.4	6.4
Histological subtype	($P < 0.01$)	($P < 0.01$)
Non-alveolar	1	1
Alveolar	2.3	2.3

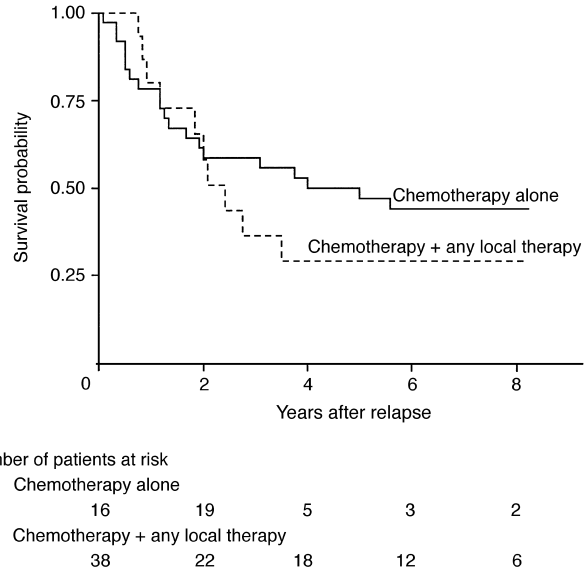

Figure 6. Five-year survival after local relapse according to the primary treatment. Treatment by chemotherapy alone (38) 46%; treatment by chemotherapy plus any kind of local therapy (16) 29%.

relapse and metastases and 2 metastases only. Among the 93 patients who received some form of local treatment, 30 (32%) relapsed (16 locally only, 5 with both local and metastatic disease and 9 with distant metastases only). The patient who died from toxicity after completion of therapy was excluded from Table 8.

Salvage therapy after relapse was chiefly determined by the primary treatment and by the site of relapse. None of the patients who developed distant metastases survived, whether metastases were associated with local relapse (7 patients) or not (11 patients). Overall, the 5-year OS from the time of an isolated local relapse ($n = 54$) was 41%, but was greater for patients treated by chemotherapy alone (46%) than for patients who had received local treatment before relapse (29%) (Figure 6).

Amongst the 54 patients with an isolated local relapse, 19 were alive in second or subsequent remission for more than 24 months after the last relapse. As a second relapse has not yet been encountered beyond that time, it is assumed that these patients are likely to be cured. Treatment for relapse in these survivors included chemotherapy in 15/19 (high-dose chemotherapy with bone marrow transplant in 3) and 4/19 underwent extensive surgery (1 orbital exenteration, 1 cystectomy, 1 middle ear exenteration, 1 nephrectomy). 7 patients received radiation therapy to a field encompassing the volume of the relapse, whilst 8 patients had more limited local treatment (surgery 1, radiation therapy to a residual volume in 2 and conservative surgery with radiation therapy in 5). Only 1 of the patients who received radiotherapy for relapse had already had previous irradiation.

Burden of therapy

The aims of the study were not only to determine whether the survival of children with rhabdomyosarcoma could be increased, but also to improve their subsequent quality of life by reducing the sequelae of treatment. To evaluate the total burden of therapy received by survivors, it is important to consider not only the nature of the treatment given as primary therapy but also that needed to retrieve patients who relapse.

Table 8. Characteristics and outcome of relapses according to modalities of initial treatment (only to 169 patients who achieved initial control)

Initial therapy	No. of patients	Alive in first complete remission	Modalities of relapse: Local relapse	Local relapse + metastases	Metastases	Alive in complete remission after relapse
CT alone after incomplete S or biopsy	76	34	38	2	2	15
CT + initial conservative S + CT	34	28	3	2	1	1
CT + RT to residual tumour (± limited S)	8	3	3		2	2
CT + limited S	8	4	3		1	1
CT + RT to initial volume	24	16	2	3	3	—
CT + S before RT to initial volume	7	5	1		1	—
CT + radical S	12	7	4		1	—
Total	169 (+ 1 toxic death)	97	54*	7	11	19

CT, chemotherapy; S, surgery; RT, radiation therapy. *Of these 54 local relapses, 47 occurred at the primary site, three in the locoregional nodes and four in both primary site and locoregional nodes.

97 patients were alive in first remission (Table 8), of whom 28 were treated by primary complete surgery followed by three IVA courses; 34 had incomplete but conservative surgery or biopsy followed by chemotherapy without radiotherapy; 7 were treated by chemotherapy and additional local treatment to residual tumour (conservative surgery, 4 or brachytherapy, 3). The other 28 patients received chemotherapy followed by radiotherapy to the initial tumour volume [16], radical surgery [7], or surgery before radiotherapy to the initial tumour volume [5].

Details of the therapy given at the time of relapse to the 19 patients who were subsequent long-term survivors have been given above.

Of the 116 presumably cured patients (97 in first remission and 19 in further remission) and taking into account both the first and any subsequent treatment, 24% (28/116) had initial complete conservative surgery and chemotherapy; 29% (34/116) received chemotherapy alone after biopsy or incomplete surgery but without further local treatment; and 13% (15/116) were given chemotherapy with conservative surgery or brachytherapy for a residual mass. Only 34% (39/116) received intensive local treatment, namely extended local irradiation and/or extensive surgery.

In total, 37/116 (32%) of the cured patients received radiotherapy: 9 because of high-risk parameningeal disease, 15 because of failure to achieve a complete response to chemotherapy (radiation was only delivered to the residual volume in 3 of these patients) and 13 because of local relapse.

Overall, 34 patients with localised rhabdomyosarcoma were cured by chemotherapy alone after limited initial surgery at diagnosis and did not receive further local treatment. Table 9 shows the characteristics of these patients by site, tumour size, postsurgical residual and chemotherapy received.

Toxicity

Myelosuppression was the most common toxicity, seen after almost half of the courses of chemotherapy. However, only 26 (14%) of the patients experienced documented infection during treatment. 8 patients had a protracted interval between courses and 2 required reduced doses of chemotherapy because of poor haematological tolerance. There were 2 toxic deaths (1%): 1 due to septicaemia before the patient achieved complete remission and one because of doxorubicin-related cardiac toxicity. 11 patients (6%) experienced haematuria during therapy, in spite of the prophylactic use of Mesna, but in all cases ifosfamide could be continued after additional hydration. 4 patients had acute tubular damage during therapy leading to substitution of ifosfamide by cyclophosphamide. 5 patients experienced

Table 9. Characteristics of the 34 patients who were treated by chemotherapy alone after incomplete surgery and were alive in first remission

	Age at diagnosis (years)	Initial surgery	T status	Size (cm)	No. of courses of IVA	No. of courses of DP
Orbit ($n=9$)	6	Biopsy only	2	< 5	10	
	7	Biopsy only	2	< 5	10	
	11	Biopsy only	2	< 5	10	
	1	Biopsy only	1	< 5	3	6
	3	Biopsy only	1	un.	5	6
	7	Macro residue	1	< 5	6	
	5	Micro residue	2	< 5	10	
	7	Micro residue	2	< 5	10	
	2	Micro residue	1	< 5	6	
Non-parameningeal head and neck ($n=5$)	5	Biopsy only	1	< 5	6	
	2	Macro residue	2	> 5	10	
	6	Micro residue	2	> 5	6	
	< 1	Micro residue	2	> 5	10	
	4	Micro residue	1	< 5	6	
Parameningeal head and neck ($n=4$)	1	Biopsy only	2	< 5	10	
	3	Biopsy only	2	un.	10	
	4	Biopsy only	2	un.	5	
	5	Biopsy only	2	un.	10	
Bladder/prostate ($n=3$)	< 1	Biopsy only	2	< 5	10	
	1	Biopsy only	2	> 5	5	6
	2	Biopsy only	2	< 5	9	6
Genito-urinary non-bladder/ prostate ($n=4$)	< 1	Micro residue	2	< 5	6	
	4	Micro residue	2	< 5	10	
	7	Micro residue	1	< 5	6	
	8	Micro residue	2	< 5	6	
Limbs ($n=5$)	< 1	Micro residue	1	> 5	6	
	1	Micro residue	1	> 5	6	
	6	Micro residue	1	un.	6	
	8	Micro residue	2	> 5	10	
	15	Micro residue	1	< 5	6	
Other sites ($n=4$)	2	Biopsy only	2	> 5	10	
	5	Biopsy only	2	> 5	10	
	3	Macro residue	2	< 5	10	
	2	Micro residue	2	> 5	6	

IVA, ifosfamide, vincristine, actinomycin D; DP, doxorubicin, cisplatin; un, unknown.

seizures and 5 had significant vincristine-related neuropathy. Symptoms of encephalopathy were observed in 2 patients, for whom cyclophosphamide was substituted for ifosfamide in subsequent courses of treatment. 2 of the 52 patients who received doxorubicin as part of second-line therapy experienced cardiac failure, fatal in 1 (as above).

The follow-up of these patients is still too short for a valid assessment of the late effects from therapy. This will be studied in adult survivors when there is adequate follow-up for the development of late sequelae from radiation therapy and will be available for assessment of fertility. However, renal function was assessed in patients who had received IVA chemotherapy without cisplatin. Evaluation was performed at least 1 year after completion of therapy and the results have been published previously [18]. Among the 74 assessable patients, 4 (5%) had Fanconi's tubulopathy syndrome and 2 required treatment for more than 1 year. 5 (7%) had a low tubular phosphate re-absorption level with an elevated urinary β2 microglobulin level. 7 (9%) other patients only excreted a moderately elevated levels of β2 microglobulin, without other abnormalities [18].

With a median follow-up of 9 years, no second cancers have yet been observed.

DISCUSSION

The main goal of MMT84 was to improve treatment outcome for children with rhabdomyosarcoma. This was achieved for patients with non-metastatic disease reported here. Five-year OS increased by 16% compared with RMS75 (68 versus 52%), even though EFS was similar in the two studies (52 versus 47%) [2]. This is explained by the different approach to treatment used in the two studies. In RMS75, of the patients who received radiotherapy or underwent extensive surgery to achieve first remission (i.e. excluding patients with completely resected tumour at diagnosis and those included in the arm of the randomised trial based on primary chemotherapy), only 4% of those who experienced a local relapse were cured. In the MMT84 study, in which the majority (48/61 = 79%) of patients with local relapse had not received radiotherapy as part of their initial therapy, 17 (35%) achieved a long-term second remission after further chemotherapy, radiotherapy ± surgery. In fact, the 68% OS rate in MMT84 was similar to the survival rates reported from the IRS II study (71%) and the German CWS 81 study (73%) [19, 20]; EFS (52%) was lower than the progression-free survivals observed in IRS II and in CWS 81 (62% and 68%, respectively). The differences relate to a higher risk of local relapse—34% in MMT84 compared with 17% in CWS 81 and 15% in IRS II [19, 20]—and the greater possibility of successful salvage therapy if neither radiotherapy nor radical surgery has been used.

Patients with completely resected localised disease (stage IpT1, IpT2) treated by three courses of IVA over a period of 2 months had an excellent survival (89%) which compared favourably with the results observed in the RMS75 study using a more intensive and longer chemotherapy schedule (4 VAC + 4 VAD). This group of patients matches the criteria for clinical group I patients in the IRS (85% in IRS II and 93% in IRS III) and CWS (88%) studies, but with the inclusion of all histological subtypes [19–21]. However, the SIOP patients received shorter chemotherapy (two cycles over 2 months) and the same patients treated in the IRS II study would have received either vincristine plus actinomycin D or vincristine plus actinomycin D plus cyclophosphamide for 2 years. Alkylating agents were subsequently removed from the treatment schedule in the IRS III study and the treatment duration with vincristine plus actinomycin D reduced to 1 year [21]. In the German study, the patients would have received a 35-week chemotherapy regimen containing vincristine, actinomycin D, cyclophosphamide and doxorubicin (VACA) [20]. A more detailed comparison of results between studies for other groups of patients is difficult because treatment grouping classifications were different.

The overall improvement in survival compared with the RMS75 study was achieved despite a reduction in the use of local therapy in patients who showed a good response to initial chemotherapy. In RMS75, as in the other published collaborative studies, all patients with microscopic or macroscopic tumour after initial surgery received radiotherapy [7]. In the corresponding IRS and CWS studies, patients with incomplete initial surgery represented the great majority (85% (702/827), 76% (132/174) of whom nearly all would have received radiation therapy [19, 20]. Few of these would have had curative local therapy after relapse.

The results from MMT84 confirm that tumour site is strongly correlated with outcome, orbit and genito-urinary non-bladder/prostate sites having the most favourable prognosis, followed, in order, by bladder/prostate, head and neck, limbs and 'other' sites. This prognostic sequence is the same as that observed in the IRS III study and differs only slightly from the German experience [20, 21]. Staging strategies differed at different sites between studies, particularly in respect of lymph node sampling in paratesticular tumours. A previously published comparison of patients treated in MMT84 and other protocols (IRS III, CWS81, Italy79) concluded that diagnostic lymphadenectomy is unnecessary at presentation if there is no evidence of clinical or radiological node involvement [22].

The results of treatment of orbital rhabdomyosarcoma and other malignant mesenchymal tumours in MMT84 have already been published [23]. The 4-year OS was 86% and EFS was 62%. Further analysis of survival for these patients with longer follow-up confirmed that 9/20 (45%) of these patients were cured after treatment by chemotherapy alone, without surgery or radiation therapy. Their experience of late effects of radiation therapy for orbital tumours has recently been published by the IRS group. The affected eye was dry in 47% of the patients and was painful in 29%; 30% had unilateral ptosis, 10% had chronic corneal ulceration. Eighty-two per cent of the patients had a unilateral cataract and 72% reduced visual acuity in the affected eye, despite the fact that 67% underwent cataract extraction. A hypoplastic orbit was reported in 66% of the patients [24]. With a median age of around 5 years at the time of radiation therapy for these orbital tumours, orbital hypoplasia may be severe at the completion of growth and require plastic surgical correction.

A retrospective meta-analysis of 230 children with parameningeal rhabdomyosarcoma has been undertaken for patients in the large co-operative studies [25]. This showed that OS and EFS were both better for patients treated in IRS III than for the European groups (SIOP MMT84, German CWS, and Italian ICS studies). Low-risk patients had a better prognosis in IRS III, whilst high-risk patients had similar survival in all studies. This difference could be related to the systematic use of radiation, to the inclusion of patients with smaller tumours and to the routine use of quality control of

radiation technique in the IRS study [24]. However, the conclusions of this study led us to modify the indications of irradiation in the subsequent MMT89 SIOP study. In that study, all children who were 3 years old or older were given radiation therapy.

The MMT84 protocol stipulated that complete remission subsequently obtained by chemotherapy alone in patients after conservative but incomplete resection of tumour at diagnosis (or after initial biopsy only) should be surgically assessed whenever possible. The results of these second look surgical procedures have been published separately and include data for patients with non-rhabdomyosarcoma MMT in addition to rhabdomyosarcoma [26]. The conclusions were that positive biopsies in patients in complete clinical remission were rare (5%) and that local relapse rate remained high even when biopsy apparently confirmed complete remission. Subsequently the MMT studies have been more cautious about the value of second look surgery to confirm clinical and radiological evidence of remission.

Treatment was not stratified by histology, although the alveolar subtype emerged as an adverse prognostic factor in both univariate and multivariate analysis. This unfavourable effect has been found in other studies [27, 28], although not in the recent German experience [20] or in the IRS III study, which contrasts with the previous IRS I and IRS II studies [27] and with the international workshop recently published [29]. It has been suggested that the more intensive therapy used for these patients in IRS III may have reduced the adverse impact of alveolar subtype on clinical outcome [21].

The results of MMT84 influenced the design of the subsequent SIOP MMT89 study whose objectives, for patients with localised disease, were to determine: (1) whether an increase in dose intensity by increasing the dose of ifosfamide from 6 to 9 g/m^2/course could improve the complete remission rate achieved by chemotherapy alone; (2) whether systematic and earlier radiation therapy could improve the outcome of children older than 3 years with parameningeal tumour; (3) whether the intensification of chemotherapy by the addition of epirubicin, carboplatin and etoposide (VP16) to the IVA regimen could improve the outcome for patients with nodal involvement and for patients younger than 3 years old with parameningeal tumour who would not receive systematic radiation therapy.

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