

Singapore Rhabdomyosarcoma (RMS) Experience: Shall We Change Our Practice?

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Abstract

Introduction: Although rhabdomyosarcoma (RMS) constitutes nearly 4% of all children diagnosed with cancer in the ethnically diverse small island city of Singapore, it is unknown how children with RMS fare. **Materials and Methods:** This study investigated 50 children with RMS from April 1993 to December 2010 from KK Women's and Children's Hospital (KKH) and National University Hospital (NUH). They were treated either as per Intergroup Rhabdomyosarcoma Study Group (IRSG) or Société Internationale Pédiatrique D'Oncologie (SIOP) regimens. **Results:** Median age of diagnosis was 5.1 years (range, 0.1 to 17.3 years) with a median follow-up of 3.3 years (range, 0.4 to 15.6 years). According to IRSG classification, 18 (36%) were staged as low-risk (LR); 19 (38%) were intermediate-risk (IR), 12 (24%) were high-risk (HR) and it was unknown in 1 patient. Twenty-nine (58%) were of embryonal subtype, 17 (34%) were alveolar and subclassification was not available in 4. The primary sites of tumour were: head and neck region (n = 22); genitourinary (n = 19); extremity (n = 10); and abdomen/retroperitoneal (n = 5). At the time of analysis, 80% were alive with no evidence of disease, 9 were dead of disease, and 2 were alive with disease. By disease risk group, the 5-year event-free survival (EFS) for LR group disease was 81.3% (95% CI, 62.0 to 100.0), IR group was 61.4% (95% CI, 32.3 to 90.4) and HR group was 25.0% (95% CI, 0.0 to 49.5) respectively ($P < 0.001$). The 5-year EFS for risk by chemotherapy received as per SIOP vs per IRSG revealed: LR 83.3% vs 75.0% ($P = 0.787$); IR 83.3% vs 43.8% ($P = 0.351$); HR 0.0% vs 42.9% ($P = 0.336$) respectively. Of 15 relapses (HR, n = 7), at median of 2 years, 4 of 6 patients treated as per SIOP regimen were dead of disease and 3 of 8 treated as per IRSG were alive. **Conclusion:** Radiation therapy (RT) can be avoided in LR classification although those in higher risk classification need RT to local and distant metastatic disease. The outcome of children with RMS in Singapore can be further improved by coming together as a cooperative group to provide the best total care. Improved communication, multidisciplinary team collaboration, standardisation of protocols and rigorous data collection are keys.

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Key words: Sarcoma, Survival, Treatment

Introduction

Rhabdomyosarcoma (RMS) constitutes nearly 4% of all children diagnosed with cancer in the ethnically diverse small island city of Singapore.¹ It is the most common primary soft tissue malignancy of childhood and one which is highly sensitive to chemotherapy and radiation therapy leading to excellent overall survivals.²⁻⁵ In KK Women's and Children's Hospital (KKH), majority of the children were treated according to the European Société Internationale Pédiatrique D'Oncologie (SIOP) regimen whilst in National University Hospital (NUH), children were treated as per the American Intergroup Rhabdomyosarcoma Study Group

(IRSG) regimen as described elsewhere.⁵⁻¹¹ The 2 regimens differ in the use of radiation therapy (RT) as a salvage treatment modality for relapsed disease in the former versus upfront radiation in all alveolar and higher risk disease in the latter. Several clinical and disease characteristics predict the outcome in children with RMS including age at diagnosis, stage, group, location of primary tumour and histology. According to the IRSG, staging is done in 3 basic steps: presurgical staging based on imaging studies, postsurgical grouping and finally risk group. Risk is divided into 3 prognostic groups, low-risk (LR), intermediate-risk

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Table 1. Intergroup Rhabdomyosarcoma Staging Group Risk Classification

IRSG Pre-Treatment Staging Classification					
Stage	Site	Tumour (T)	Size	Node (N)	Metastasis (M)
I	Orbit, head and neck (excluding parameningeal) GU: non-bladder/nonprostate	T1 or T2	a or b	N0, N1, or Nx	M0
II	Bladder/prostate, extremity, cranial, parameningeal, other (includes trunk, retroperitoneum, and so on)	T1 or T2	a	N0 or Nx	M0
III	Bladder/prostate, extremity, cranial, parameningeal, other (includes trunk, retroperitoneum, and so on)	T1 or T2	a b	N1 N0, N1, or Nx	M0 M0
IV	All	T1 or T2	a or b	N0 or N1	M1
Notes Tumour: T1, confined to anatomic site of origin, (a) ≤ 5 cm in diameter in size, (b) ≥ 5 cm in diameter in size; T2, extension and/or fixative to surrounding tissue; regional nodes: N0, regional nodes clinically not involved; N1, regional nodes clinically involved by neoplasm; Nx, clinical status of regional nodes unknown; metastasis: M0, no distant metastasis; M1, metastasis present					
IRSG Surgical-Pathological Grouping Classification			IRSG Risk Classification		
Group 1	Localised disease, completely excised, no microscopic residual			Embryonal	
A	Confined to site of origin, completely resected		Low	Group I, II	
B	Infiltrating beyond site of origin, completely resected			Group III, stage I	
Group 2	Total gross resection			Embryonal	
A	Gross resection with evidence of microscopic local residual			Group III, stage 2, 3 (unfavourable sites)	
B	Regional disease with involved lymph nodes, completely resected with no microscopic residual		Intermediate	Group IV age <10 years	
C	Microscopic local and/or nodal residual			Alveolar	
				Groups I-III	
Group 3	Incomplete resection or biopsy with gross residual				
Group 4	Distant metastases		High	Group IV (excluding embryonal <10 years)	

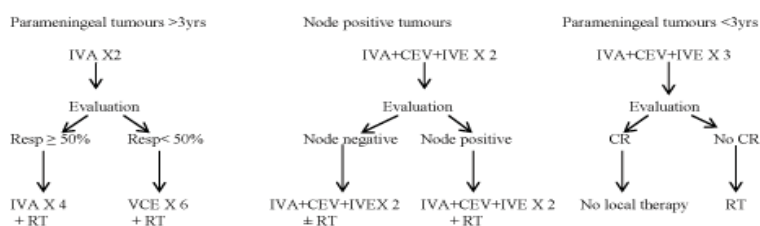
(IR), or high-risk (HR) subgroups based on estimated failure-free survival differences (Table 1).¹²

We set out to investigate the patient and tumour characteristics and the outcome based on the 2 varied regimens used in the care of these children diagnosed with this uncommon disease in Singapore.

Materials and Methods

This was a detailed retrospective chart review of all children and young adolescents diagnosed and treated with RMS in the Departments of Paediatric Haematology-Oncology, KKH and NUH. Data abstraction included patient demographics such as age at diagnosis, gender, race, disease characteristics, and types of treatments received. In addition to a detailed history and physical examination, staging evaluation included a number of tests. Primary tumour imaging was performed by magnetic resonance imaging (MRI) or computerised tomography (CT) scans. Metastatic disease workup included CT scan of the thorax, a bone scan, bilateral bone marrow and trephine biopsies and a lumbar puncture if the primary tumour was in a central nervous system location.

Presently, children diagnosed with RMS in Singapore are treated as per the SIOP regimen or as per the IRSG regimen depending on the treating physician's decision. The 2 regimens differ in the avoidance of RT in the former and its use as an upfront therapy in the latter. The approach by IRSG is to treat the systemic disease with a multimodality therapy, and to aim for maximum initial function sparing surgery. Local therapy, either surgical resection and/or RT is required for any disease visible by diagnostic imaging at primary or metastatic sites. RT is also given for any postoperative microscopic and gross residual disease and all alveolar subtype. All patients received chemotherapy whilst intensity, duration, and the number of drugs varied by IRSG classification risk factors (Fig. 1).⁷ Therapy spanning over 48 weeks is the standard of care. SIOP regimen's goal, on the other hand, is to avoid local therapy with radiation to diminish its late effects. Therapy duration varies from 3 to 6 months depending on whether the disease results in partial response (PR) or progressive disease (PD) at interim evaluation by imaging studies. If there were a complete response (CR), RT is omitted whilst RT will be given to those with PR or PD status after second-line chemotherapy (Fig. 1).⁹ CR is defined in our study as the

Treatment Schedule for Société Internationale d'Oncologie Pédiatrique (SIOP)

Abbreviations: IVA: ifosfamide, vincristine, actinomycin-D; CEV: carboplatin, epirubicin, vincristine; Resp: response; CR: complete remission; RT: radiation therapy; VCE: vincristine, carboplatin, epidophyllotoxin; IVE: ifosfamide, vincristine, etoposide

Adapted from Stevens MC, et al. *J Clin Oncol* 2005;23:2618-28³

Treatment Roadmap for Intergroup Rhabdomyosarcoma Study Group (IRSG)**Intermediate Risk**

VAC Day 1 of weeks 0, 3, 6, 9, 12, 21, 24, 27, 30, 33
 V Day 1 of weeks 1, 2, 4, 5, 7, 8, 10, 11, 13, 14, 16, 17, 19, 20, 22, 23, 25, 26, 28, 29, 31, 32, 34, 35
 VC Day 1 of weeks 15, 18 during RT
 Evaluation weeks 12, 24, 35

Abbreviations: VAC: vincristine, actinomycin-D, cyclophosphamide; V: vincristine; VC: vincristine, cyclophosphamide; RT: radiation therapy

Adapted from Crist WM, et al. *J Clin Oncol* 2001;19:3091-102⁷

Fig. 1. The chemotherapy regimens.

disappearance of all tumour(s) with no evidence of disease. PR is defined as the following: $\geq 50\%$ decrease in the sum of the products of the maximum perpendicular diameters of all measurable lesions; there is no evidence of progression in any lesion; and no new lesions are found. Lastly, PD is defined as $\geq 25\%$ increase in the sum of the products of the maximum perpendicular diameters of measurable lesions at any involved site and/or the appearance of new lesions.

Statistical Analysis

All analyses were performed using SPSS 15.0. Descriptive statistics for quantitative variables were presented as median (range) and n (%) for qualitative variables. The clinical primary endpoint of this study was adverse event free survival. This was defined as the time of entry into the study or time at diagnosis to the disease progression, occurrence of a metastatic disease, death from non-disease causes, development of a second malignant neoplasm, or last follow-up. Disease free survival and overall survivals were calculated using the method of Kaplan-Meier analysis.¹³ Log-rank test was performed to compare the disease free and overall survival for metastatic site, chemotherapy and amputation. Statistical significance was set at $P < 0.05$.

Results

Fifty patients with primary RMS are reported here. The median follow-up was 3.3 years (range, 0.4 to 15.6 years). The median age at diagnosis was 5.1 years (range, 0.1 to 17.3 years). Twenty-eight (56.0%) children were diagnosed

with RMS below the age of 6 years or younger with 15 (30.0%) of them being diagnosed under the age of 2 years. Head and neck primary was the most prevalent with a total of 19 patients. The common primary location in the head and neck was orbital in 5, non-orbital in 13 patients and 1 in the parameningeal region. The next most common site for the primary RMS was in the genitourinary tract with 17 patients; non-bladder in 8, bladder in 1, testes in 7, and prostate in 1. Extremities were the primary site in 8 patients; retroperitoneum in 3; spine in 2; and pancreas in 1. Histology as confirmed by biopsy of the primary tumour, was more common in embryonal subtype (E-RMS) in 29 (58.0%) patients; alveolar (A-RMS) in 17 (34.0%) and information was unable to be determined in 4 patients. Of the 17 patients with A-RMS, 9 were in the head and neck region (orbit = 3) and 3 involved the extremity. Of the 8 tumours in the extremity, 5 were embryonal and 3 were alveolar. According to the IRSG risk group, 18 (36.0%) were LR, 19 (38.0%) were IR, 12 (24.0%) were HR. Risk group was unknown in 1. Twenty-eight patients received chemotherapy as per the IRSG, 19 as per SIOP, 2 patients' treatment regimen was unknown and 1 received a combination of vincristine, etoposide, platinum, cyclophosphamide (VETOPEC)¹⁴ (Table 2).

Chemotherapy and Disease Response Status

In the study cohort, 28 (57.1%) patients were treated as per the IRSG regimen while 18 (36.7%) were as per the SIOP regimen and 3 were treated as per other regimens (Table 3). Of the 28 patients treated as per the IRSG regimen, 10

Table 2. Patient and Tumour Characteristics

	<u>Low-Risk (n = 18)</u>			<u>Intermediate-Risk (n = 19)</u>			<u>High-Risk (n = 12)</u>	
	IRSG (10)	SIOP (6)	Other (2)	IRSG (11)	SIOP (7)	Other (1)	IRSG (7)	SIOP (5)
Age (years)								
<1	1	2	1	1	2		1	1
1 to 4	5	1	1	2	3		1	2
5 to 9	1	2		6	1		1	
10 to 14	1			2	1	1	3	2
≥15 and above	2	1					1	
Histology								
Alveolar (17)	1			6	2	1	3	4
Embryonal (29)	7	6	1	5	4		3	1
Other/Unknown (5)	2	1					1	
Site Primary								
Orbit		1		2	1			
Head/Neck	3			4	2		1	3
Parameningeal				1				
GU B/P				3	3		1	
GU non B/P	4	5	1			1	1	
Extremity	1	1	1	1	1		1	1
Other	1						3	1
CR (39)	8	5	1	11	7		3	2
RT (21)								
Yes	1	1		9	4		3	3
Relapsed (15)								
Local	2	1		3	1		2	1
Metastatic (both)				0 (1)	0 (1)		1	3
Stats								
ANED (AWD)	9	6		9	6 (1)		4	0
DOD	1			2			3	4

ANED: Alive no evidence of disease; AWD: Alive with disease; B/P: Bladder and prostate; CR: Complete response; DOD: Dead of disease; GU: Genitourinary; IRSG: Intergroup Rhabdomyosarcoma Study Group; SIOP: Société Internationale d'Oncologie Pédiatrique

(35.7%) were in the LR group; 11 (39.3%) were in the IR group; and 7 (25.0%) were in the HR group. Complete response status as determined by CT or MRI imaging studies at the end of primary therapy was achieved in 8 of 10 (80.0%) in the LR group; all 11 (100.0%) in the IR group; and 3 of 7 (42.9%) in the HR group. Five (17.9%) of 28 patients treated as per the IRSG regimen achieved PR; 4 were from the HR group. In the 18 patients treated as per the SIOP regimen, 6 (33.3%) were in the LR group; 7 (38.9%) in the IR group; and 5 (27.8%) were in the HR group. CR status was achieved at the end of primary therapy in 5 (83.3%) in the LR group; all 7 (100.0%) in the IR group; and 2 (40.0%) in the HR group. Four of 18 (22.2%) patients treated as per the SIOP regimen achieved PR status; 3 were from the HR group (Table 3). The risk group of 1 patient treated as per SIOP regimen was unknown (no. 50). Every attempt was

made to adhere to the standard treatment protocols in all 50 patients. There were no reported treatment-related deaths.

Radiation Therapy

From the whole cohort of 50 patients, a total of 21 (42.0%) patients received chemotherapy and upfront RT. By risk group, 2 (11.1%) patients received both chemotherapy and upfront RT for their primary therapy in the LR group. In the 19 patients from the IR group, 13 (68.4%) received both chemotherapy and upfront RT and all achieved CR. In the 12 patients from the HR group, half of the patients received upfront RT and chemotherapy; 4 of whom achieved CR and 2 achieved PR at the end of primary therapy (Table 3). Of the 21 patients who received RT, 13 patients were treated as per the IRSG regimen and 8 patients were treated as

Table 3. Patient and Tumour Characteristics of All Patients by Risk Status

No.	Age	Histology	Site (primary)	Therapy (primary)	Relapse Site	Dx-FU (years)	Dx-R1 (years)	Status (primary)	Status Last FU	Therapy Relapse
Low-Risk										
1	4.1	A-RMS	extremity	IRSG		0.7		CR	ANED	
2	15.5	RMS	GU (testes)	IRSG		1.3		CR	ANED	
3	1.6	E-RMS	GU	IRSG	local	2.0	2.0	PR	DOD	Unk
4	6.3	E-RMS	retroperitoneum	IRSG+RT	Unk	2.4	2.1	Unk	ANED	Unk
5	12.1	E-RMS	HN (ear)	IRSG		2.6		CR	ANED	
6	1.6	E-RMS	GU	IRSG		5.9		CR	ANED	
7	2.4	E-RMS	HN	IRSG		7.0		CR	ANED	
8	17.1	E-RMS	GU (testes)	IRSG		8.4		CR	ANED	
9	2.8	RMS	HN (lip)	IRSG		8.8		CR	ANED	
10	0.5	E-RMS	extremity	IRSG		12.2		CR	ANED	
11	0.1	E-RMS	GU (testes)	SIOP		2.7		CR	ANED	
12	9.6	E-RMS	extremity	SIOP		3.9		CR	ANED	
13	3.5	E-RMS	GU	SIOP		4.7		CR	ANED	
14	15.4	E-RMS	GU (testes)	SIOP		4.7		CR	ANED	
15	8.5	E-RMS	HN (orbit)	SIOP+RT	local	8.8	1.4	PR	ANED	CE+V+
16	0.4	E-RMS	GU (prostate)	SIOP		9.6		CR	ANED	
17	0.3	E-RMS	extremity	Unk		4.4		CR	ANED	
18	4.5	RMS	GU (testes)	Other		10.0		CR	ANED	
Intermediate-Risk										
19	13.4	A-RMS	HN (orbit)	IRSG+RT		1.4		CR	ANED	
20	6.2	E-RMS	GU (bladder)	IRSG+RT		2.0		CR	ANED	
21	1.0	A-RMS	HN (NP)	IRSG+RT		2.7		CR	ANED	
22	3.9	A-RMS	extremity	IRSG+RT		2.9		CR	ANED	
23	0.9	A-RMS	HN (NP)	IRSG		4.0		CR	ANED	
24	5.7	A-RMS	HN (NP)	IRSG+RT	local	4.4	1.3	CR	DOD	IE+RT, VI*
25	8.4	A-RMS	HN	IRSG+RT	local	4.6	2.3	CR	ANED	S+GemDoce†
26	5.7	E-RMS	GU (pelvis)	IRSG+RT	local	5.3	4.4	CR	DOD	CE+V
27	12.3	E-RMS	HN (NP)	IRSG+RT		7.7		CR	ANED	
28	6.0	E-RMS	HN (orbit)	IRSG		8.2		CR	ANED	
29	7.0	E-RMS	HN (PM)	IRSG+RT		8.6		CR	ANED	
30	0.8	E-RMS	extremity	SIOP+RT		1.4		CR	ANED	
31	3.6	E-RMS	HN (pharynx)	SIOP+RT	local	1.6	1.5	CR	AWD	CarboplatinV
32	3.9	E-RMS	HN (ear)	SIOP		1.9		CR	ANED	
33	13.6	A-RMS	GU (perineum)	SIOP+RT		1.9		CR	ANED	
34	9.8	A-RMS	HN (orbit)	SIOP+RT		3.8		CR	ANED	
35	0.2	E-RMS	GU (pelvis)	SIOP		6.3		CR	ANED	
36	16.3	A-RMS	GU (testes)	VETOPEC	local	7.8	7.8	CR	AWD	None
37	3.3	E-RMS	GU (pelvis)	SIOP		15.6		CR	ANED	

Table 3. Patient and Tumour Characteristics of All Patients by Risk Status (Con't)

No.	Age	Histology	Site (primary)	Therapy (primary)	Relapse Site	Dx-FU (years)	Dx-R1 (years)	Status (primary)	Status Last FU	Therapy Relapse
High-Risk										
38	9.5	RMS	retroperitoneum	IRSG		0.4		PR	DOD	
39	0.8	E-RMS	pancreas	IRSG	local	0.8	0.8	PR	DOD	Unk
40	14.8	E-RMS	GU (pelvis)	IRSG	local	1.0	0.4	PR	DOD	VI*CT
41	12.5	E-RMS	HN (NP)	IRSG+RT	local	2.2	1.6	PR	ANED	Unk
42	1.6	A-RMS	extremity	IRSG		2.5		CR	ANED	
43	11.9	A-RMS	spine	IRSG+RT		2.5		CR	ANED	
44	17.3	A-RMS	GU (testes)	IRSG+RT		5.6		CR	ANED	
45	1.1	A-RMS	HN (parotid)	SIOP		0.5		PR	DOD	
46	12.4	A-RMS	HN (orbit, CNS)	SIOP+RT	brain	1.1	0.7	PR	DOD	VAC+RT, IVA
47	13.3	A-RMS	spine	SIOP+RT	leg	2.3	1.8	CR	DOD	E, VI*
48‡	3.7	A-RMS	HN	SIOP+RT	thigh	2.6	2.0	CR	DOD	CE*V
49	0.8	E-RMS	extremity	SIOP	local, mets	6.4	0.8	PR	DOD	S
Unknown										
50	0.3	RMS	retroperitoneum	SIOP		1.4			CR	ANED

A: Actinomycin-D; ANED: Alive no evidence of disease; AWD: Alive with disease; A-RMS: Alveolar rhabdomyosarcoma; C: Cyclophosphamide; CNS: Central nervous system; CR: Complete response; Doce: Docetaxol; DOD: Dead of disease; Dx: Diagnosis; E+: Epirubicin; E: Etoposide; E-RMS: Embryonal rhabdomyosarcoma; FU: Follow-up; Gem: Gemcitabine; GU: Genitourinary; HN: Head and neck; I: Ifosfamide; I*: Irinotecan; IRSG: Intergroup Rhabdomyosarcoma Study group; Mets: Metastasis; NP: Nasopharynx; PM: Parameningeal; PR: Partial response; R1: First relapse; RT: Radiation therapy; SIOP: Société Internationale d'Oncologie Pédiatrique; S: Surgery; T: Teniposide; Unk: Unknown; V: Vincristine; VETOPEC: Vincristine, Etoposide, Platinum, Cyclophosphamide

†Autologous stem cell rescue.

‡Patient suffered second relapse in lungs and liver at 0.5 years from the first relapse.

per the SIOP regimen. In the 13 patients treated as per the IRSG regimen and upfront RT, a large majority, 9 (72.6%) were from the IR group while 3 (16.7%) were from the HR group. Almost all (11 out of 13) patients treated as per IRSG regimen and upfront RT achieved CR at the end of primary therapy. From those treated as per the SIOP regimen and upfront RT, 4 (50.0%) of 8 were in the IR group and 3 (37.5%) were in the HR group. Six of 8 in this group achieved CR with chemotherapy and upfront RT. In the study cohort, 2 patients received RT as an adjuvant therapy for their relapsed disease (nos. 25 and 46). The latter patient received RT for both primary and relapsed disease.

Relapse

Fifteen patients relapsed at a median of 6.3 years (range, 0.8 to 16.3 years) with a median follow-up of 2.4 years (range, 0.8 to 8.8 years). Amongst those with relapsed disease, histology of the primary tumour was embryonal in 9 and alveolar in 6 patients; disease risk group revealed 7 in HR, 5 in IR and 3 in LR groups. Head and neck primary (orbit, n = 2) was the most common primary site with 9

(60.0%) patients out of 15, followed by the genital urinary tract primary in 4. Initial chemotherapy regimen for the primary tumour in 8 out of the 15 relapsed patients was as per the IRSG regimen, 6 were as per the SIOP regimen and 1 was as per the VETOPEC¹⁴ regimen. Although 10 (66.7%) of 15 patients who relapsed received chemotherapy and upfront RT prior to relapse; only 2 received RT as an adjuvant therapy for their relapsed disease (nos. 24 and 46). The latter patient received both upfront and adjuvant RT for their primary tumour and relapsed disease. By risk group status, 2 of the patients in LR group with residual disease at the end of primary therapy relapsed locally, no. 3 and 15. The latter patient (no. 15), received upfront RT and was alive- no evidence of disease (ANED) at last follow-up whilst the former (no. 3), who did not receive upfront or adjuvant RT was dead of disease (DOD). Five patients relapsed locally in the IR group although all patients achieved CR at the end of primary therapy and 4 received upfront RT. Two of the patients were DOD. Seven patients relapsed in the HR group; there were 2 local relapses and 5 distant metastases inclusive of 1 who relapsed both locally

and with distant relapse (no. 49). Relapsed distant metastasis was only seen in those with HR group classification. Half of the relapsed patients in HR group achieved CR at the end of primary therapy while the remaining half achieved only PR. Nine (60.0%) patients in HR group with relapsed disease were DOD, 4 were ANED and 2 were alive with disease at last follow-up. Therapy for relapsed disease varied amongst all the patients and included various combinations of chemotherapy, surgery with or without RT. Patient and tumour characteristics are as outlined in Table 3.

Survival

The 5-year event-free survival (EFS) and overall survival (OS) for the cohort were 60.4% and 80.3% respectively. By disease risk group, the 5-year EFS for LR group disease was 81.3% (95% CI, 62.0 to 100.0), IR group was 61.4% (95% CI, 32.3 to 90.4) and HR group was 25.0% (95% CI, 0.0 to 49.5) respectively ($P < 0.001$) (Figs. 2 and 3). The 5-year EFS for disease risk classification by chemotherapy received as per SIOP vs per IRSG revealed: LR–83.3% vs 75.0% ($P = 0.787$); IR–83.3% vs 43.8% ($P = 0.351$); HR–0.0% vs 42.9% ($P = 0.336$) respectively (Figs. 4 and 5). Of 15 relapses ($n = 7$ HR), at a median of 2.0 years, 4 out of 5 patients treated as per SIOP regimen were DOD and 1 whose primary was orbital site was ANED. Three (37.5%) out of 8 treated as per IRSG and RT were alive at last follow-up. The 5-year EFS and OS for those with relapsed disease by chemotherapy received revealed 0% and 0% by SIOP and 50.0% and 44.4% by IRSG regimens respectively ($P = 0.23$, and $P = 0.37$) (Figs. 6 and 7).

Discussion

The incidence of RMS in Singapore is small but children diagnosed with the disease have a good chance of survival. High-risk disease classification treated as per IRSG regimen resulted in superior event-free survival than those treated as per SIOP regimen which is clinically important although not statistically significant ($P = 0.95$). Complete resolution of the disease by imaging studies can be achieved in a majority of the patients in all 3 risk groups at the end of primary therapy when treated with either as per IRSG or the SIOP regimens. RT cannot be avoided in those with higher risk classification RMS. Although relapsed disease can be salvaged in some after initial therapy using SIOP regimen, its impact on the family is not known. In our study, the main problem concerned the use of varied treatment protocols which makes analysis of current and future outcomes challenging.

A large majority of the children, 27 (54.0%) in this cohort were diagnosed with RMS under the age of 6 years whilst 14 were diagnosed between the ages of 10 to 17 years of

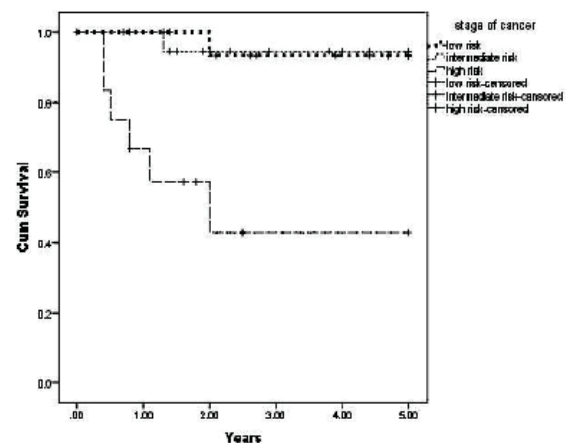


Fig. 2. Chart showing the event-free survival by disease risk status for cohort.

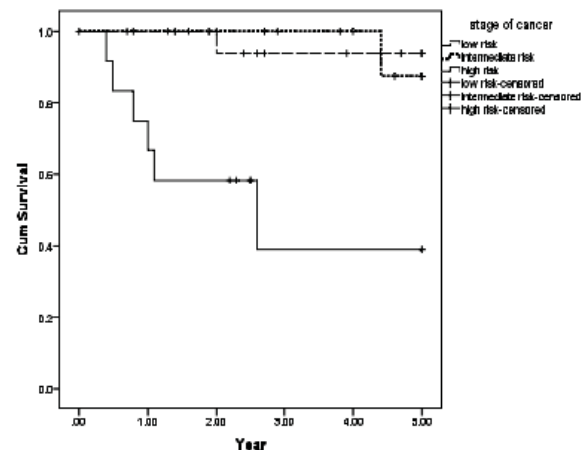


Fig. 3. Chart showing the overall survival by disease risk status for cohort.

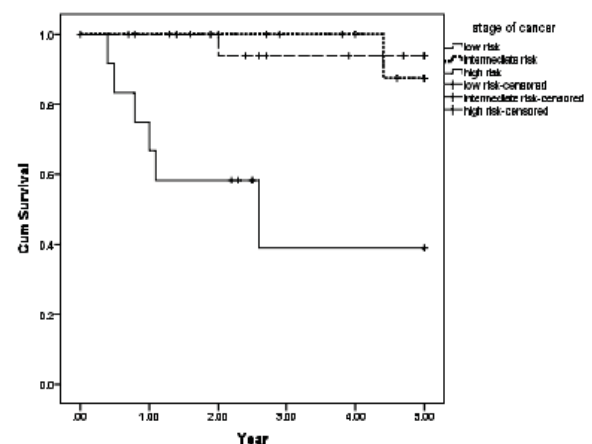


Fig. 4. Chart showing the event-free survival by chemo for high-risk patients.

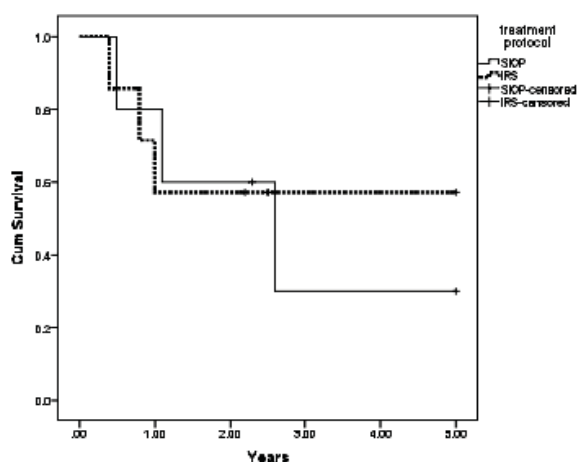


Fig. 5. Chart showing the overall survival by chemo for high-risk patients.

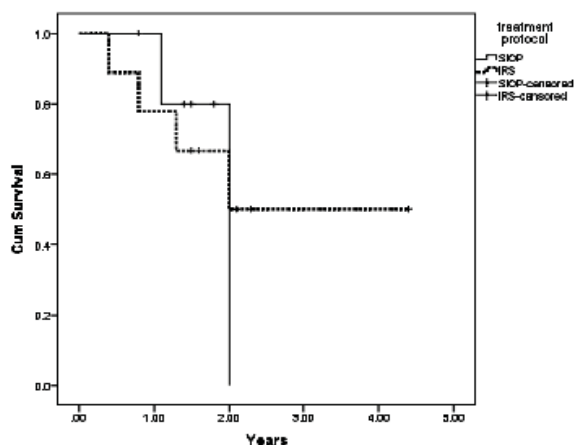


Fig. 6. Chart showing event-free survival for relapsed patients.

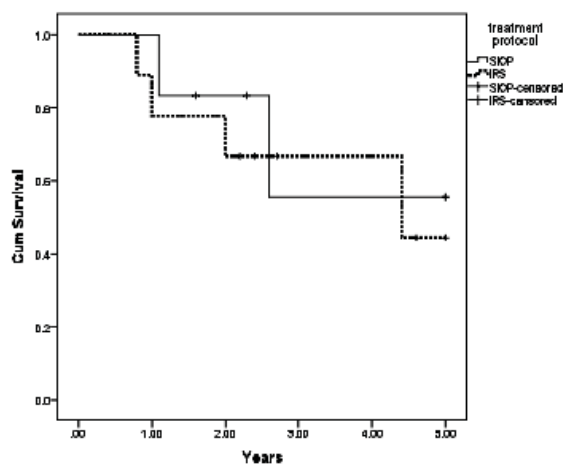


Fig. 7. Chart showing overall survival for relapsed patients.

age. Nine (18.0%) of the patients diagnosed with RMS were under the age of 1 year. Majority presented with head and neck: 19 (39.0%) primary, similar to our neighbour island city of Hong Kong.¹⁵ Histological subtype classification revealed that the embryonal RMS was more common. In our experience, embryonal subtype did better compared to those with alveolar subtype similar to international studies. However, in Hong Kong there was no difference in survival between those with embryonal versus alveolar tumours. Both our studies are limited by its retrospective nature and the small sample size. According to the IRSG risk group, majority of the children were in the IR group (38.0%). Surprisingly, a higher percentage, 24.0% of our patients presented with HR disease classification, whereas international studies approximate high-risk disease occurring at an average of 15.0%.^{6,16,17}

The 5-year EFS and OS for our cohort were higher than our neighbours with 60.4% and 80.3% respectively. In Hong Kong's experience, their 5-year EFS and OS rates for the entire cohort with a median follow-up of 3.4 years (range, 0.2 to 16.7 years), were 32.0 % (95% CI, 10.0% to 55.0%) and 49.0% (26.0% to 73.0%) respectively. Not surprisingly, patients with high-risk or metastatic tumours fared worse in all the studies. However, those with high-risk disease treated as per IRSG regimen fared better in 5-year EFS than those treated as per the SIOP regimen, although statistically not significant. It appears that those in the LR and IR groups treated as per the SIOP regimen fared slightly better (10% more) although this was not statistically significant. Those in the IR group treated as per SIOP regimen could not avoid RT which may have helped achieve excellent local control contributing towards better survival. There were 15 relapses at a median of 2 years from diagnosis, 7 of who were with high-risk disease. Only 2 out of 6 treated as per SIOP regimen were salvageable and were alive at 0.1 and 7.4 years. The latter had an orbital primary, a favourable site at diagnosis. Although every possible attempt was made to perform a detailed chart review and treatment regimens were delivered according to standard protocols for all patients at both institutions, we were limited by the retrospective nature of our analysis and the small sample size.

RT can be avoided in LR classification although those in the higher risk group (IR and HR) should receive upfront RT to both local and metastatic disease sites. One of the main philosophies of the SIOP regimen is to avoid RT in an effort to eliminate its late effects by employing it as a salvage therapy in those with less than optimal response to initial chemotherapy or in those who relapsed. On the other hand, the approach by IRSG is for upfront RT in those with all alveolar histology or those in the IR or HR disease group. In our small cohort, only a handful of patients did not achieve CR at the end of primary therapy.

One patient in LR group treated as per the SIOP regimen did not achieve CR and required RT. In the IR group, a large majority, 5 (71.4%) of 7 patients treated as per the SIOP regimen could not avoid RT and all achieved CR by the end of therapy for primary disease. For those in the HR group, despite receiving upfront RT, achieving CR or PR status did not play a role in developing either local or metastatic RMS. A larger proportion of them suffered distant relapses and succumbed to the disease. For our close neighbours in Malaysia, the protocol adopted for children with RMS is as per the SIOP regimen. According to their publication from 1981, outcome has been poor, mainly due to advanced disease at presentation and abandonment to treatment.¹⁸ Apart from a few case series on RMS, there are no later follow-up reports from the country to determine whether our outcomes are similar.¹⁹⁻²¹ Nearby, Hong Kong's experience on 19 consecutive cases of RMS, each staged and treated according to the IRSG guidelines, found that their cohort of Chinese children did less favourably than that reported in international studies. They cited that their main reason was due to a high proportion of patients with metastatic disease, i.e. those with HR RMS.¹⁵ Although we have similarly high percentage of children with HR disease at the time of diagnosis, our patients fared better.

The outcome of children with RMS in Singapore can be further improved by coming together as a cooperative group to provide the best total care. The main challenge in our study concerned the use of varied treatment regimens or protocols. One possible explanation as to why 2 different regimens were used for treatment of this rather uncommon tumour is likely as a result of treating physician's preference and the location in which their subspecialty training was received. In Japan, a geographically larger country with a more complex medical set-up and numerous hospitals, they have successfully set up a cooperative Japan Rhabdomyosarcoma Study Group (JRSG). The aim of JRSG was to improve the outcome and to establish standardised therapy for children with RMS. This move resulted after retrospective studies performed as well as analysis from the Japanese Society for Paediatric Surgery found that the survival rates of each risk group, including those in LR group were lower than those in the US or Europe.^{22,23} Singapore is a rather small country with a resident population nearing 5 million. Incidence of childhood cancer is fortunately low with even lower rates of incidence of RMS. The use of a non-standardised disease classification system and varied treatment regimen do not allow us to consistently analyse and report our outcomes. Improved communication, together with a multidisciplinary team collaboration inclusive of paediatric pathologists, paediatric radiologists, paediatric sarcoma surgeons, paediatric radiation oncologists, paediatric oncology nurses, paediatric oncologists; and rigorous and robust data collection will be the key to success.

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