Title	Treatment outcome of rhabdomyosarcoma in Hong Kong Chinese children
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ORIGINAL ARTICLE

Treatment outcome of rhabdomyosarcoma in Hong Kong Chinese children

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Objectives To review the treatment outcome of rhabdomyosarcoma in Hong Kong Chinese children.

Design Retrospective review.

Setting University teaching hospital, Hong Kong.

Patients Consecutive cases of rhabdomyosarcoma diagnosed and treated by the Department of Paediatrics and Adolescent Medicine of Queen Mary Hospital between 1989 and 2005. Each patient was staged and treated according to the Intergroup Rhabdomyosarcoma Study guidelines.

Main outcome measures Overall and event-free survival rates, and toxicity data.

Results Of 19 patients (8 males and 11 females), 14 (74%) were younger than 10 years old. The median age at diagnosis was 6 (range, 0.5-17) years. Primary sites of rhabdomyosarcoma included: the head and neck (n=8; 6 classified as cranial parameningeal), genitourinary (3), extremity (3), pelvis (3), and trunk (2). Thirteen (68%) had embryonal and six (32%) had alveolar histology. Two, 2, 9, and 6 were classified as belonging to Intergroup Rhabdomyosarcoma Study groups 1, 2, 3, and 4, respectively. Respective 5-year overall and event-free survival rates of the entire cohort were 49% (95% confidence interval, 26-73%) and 32% (10-55%), with a median follow-up of 3.4 (range, 0.2-16.7) years. In non-metastatic cases (Intergroup Rhabdomyosarcoma Study groups 1-3), the 5-year overall survival rate was 66% (95% confidence interval, 39-93%) and in metastatic cases (group 4) it was 17% (0-46%). The 5-year overall survival rate for patients aged less than 10 years was 60% (95% confidence interval, 33-87%) compared to 20% (0-55%) in those aged 10 years and over. Significant treatment-related toxicities including myelosuppression, infections, peripheral neuropathy, and second cancers were encountered.

Conclusions Treatment outcome of rhabdomyosarcoma in this cohort of Chinese children was less favourable than that reported in international studies. Whilst the main reason could have been related to the high proportion of metastatic cases, also non-metastatic cases faired worse. Improved outcomes may be achieved by advances in multidisciplinary (paediatric oncology, pathology, radiotherapy, and surgery) management and supportive care.

Key words
Adolescent; Child; Rhabdomyosarcoma; Treatment outcome

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Introduction

Rhabdomyosarcoma (RMS) is the most common paediatric soft-tissue sarcoma and accounts for approximately 4 to 5% of all childhood malignancies. The disease may appear in any organ or tissue, and can metastasise to lung, bone marrow, bone, and lymph nodes. Current treatment regimens incorporate surgery, chemotherapy, and radiotherapy (RT). Using this multimodality approach, the cure rates for RMS have steadily increased from only 25% in the 1970s to 70% in the 1990s.[1-3] The prognostic factors include: the primary site, the histology, the age at diagnosis, the clinical stage and grouping.[3-6] The Intergroup Rhabdomyosarcoma Study Group (IRSG) has conducted four consecutive clinical trials (IRS-I, 1972-78; IRS-II, 1978-84; IRS-III, 1984-91; IRS-IV, 1991-97),[3,7-9] with treatment outcomes that compared favourably with other large international studies.[3,10-12] In Hong Kong, we had largely adopted the IRSG treatment regimens. The aim of this study was to review corresponding treatment outcomes of children with RMS diagnosed at Queen Mary Hospital over the past 16 years.

香港華裔兒童橫紋肌肉瘤的治療結果

目的 回顧檢討香港華裔兒童橫紋肌肉瘤的治療結果。

設計 回顧研究。

安排 香港一所大學教學醫院。

患者 1989年至2005年間，瑪麗醫院兒科及青少年科連續診治的橫紋肌肉瘤患者；所有患者均曾按Intergroup Rhabdomyosarcoma Study (IRS)研究指引分級和治療。

主要結果測量 總生存率、無事件生存率，及有關毒性的數據。

結果 19位患者中（8男11女），14人(74%)在10歲以下，發病年齡中位數為6歲（介乎0.5至17歲）。橫紋肌肉瘤原發位置分佈在頭頸部（共8例，其中6例診斷為腦膜旁）、泌尿生殖器（3例）、肢體（3例）、骨盆（3例）、軀幹（2例）。13例(68%)屬胚胎形組織，6例(32%)屬泡狀組織。按研究指引把患者歸為四個IRS組別，第一組有2人，第二組有2人，第三組有9人，第四組有6人。整個群組計，5年總生存率為49%（95%置信區間：26-73%），無事件生存率為32% (10-55%)，中位隨訪期為3.4年（介乎0.2至16.7年）。非轉移性病例（即IRS第一至三組）5年整體存活率有66%（95%置信區間：39-93%），轉移性病例（即IRS第四組）的則只有17% (0-46%)。10歲以下患者的5年整體存活率有60%（95%置信區間：33-87%），10歲或以上的患者只有20% (0-55%)。明顯在患者身上可見，與治療相關的毒性現象包括骨髓抑制、感染、周圍性神經病變、二次癌症。

結論 比對國際的研究數據，這次香港華裔兒童橫紋肌肉瘤研究所見的治療結果並不理想，原因固然是和相當多病例屬轉移性有關，但非轉移性病例的治療效果同樣強差人意。跨科治理（兒童腫瘤科、病理學、放射治療學和外科的合作）以及有效的護理支援，可能有助提升療效。

Methods

Patients

Consecutive patients younger than the age of 18 years, with RMS diagnosed and treated at Queen Mary Hospital between 1989 and 2005, were identified from our clinical database. Charts were reviewed to extract demographic data, clinical features, treatment protocols, toxicity, and outcomes. Twenty-two patients with RMS presented to our hospital. Three patients were excluded because they subsequently received treatment in other medical centres; the remaining 19 formed the subjects of this study. Seventeen children were treated with the IRS-IV protocol,[3] one patient with the IRS-V protocol[13] and one with the International Society of Paediatric Oncology Malignant Mesenchymal Tumour (SIOP MMT)–89 protocol.[11]

Definitions

Overall survival (OS) was defined as the time from the start of treatment to death from any cause. Events were defined as disease relapse or second neoplasm after complete remission or death from any cause. The censor date was 31 March 2006. Patients were assigned presurgical staging based on the primary tumour site, size, presence or absence of clinically evident lymph node involvement and/or metastatic disease, according to the IRSG presurgical staging classification.[3] Patients were also assigned clinical grouping according to the surgical-pathological system of the IRSG postsurgical grouping classification.[3] Toxicities were evaluated by the National Cancer Institute–Common Toxicity Criteria (NCI-CTC) version 2.0.[14] Histological diagnoses of all 19 RMS cases were validated by two pathologists (SKC, TWHS), who retrieved and reviewed the original diagnostic slides, according to the International Classification of Rhabdomyosarcoma.[4]

Statistical methods

Overall survival and event-free survival (EFS) rates were calculated using the Kaplan-Meier method. Since our study involved a relatively small number of patients in a single institution, subgroup analysis of known prognostic factors was not performed.

Results

Patient characteristics

Fourteen (74%) of the 19 patients were less than 10 years old; their median age at diagnosis was 6 (range, 0.5-17) years, eight were male and 11 female. One child had neurofibromatosis. Our patients had diverse clinical presentations, depending on the site of the primary tumour, ranging from an indolent painlessly enlarging mass to an acute onset with cranial nerve palsy, spinal cord compression, bleeding, and gastrointestinal or urinary tract obstruction. The most common primary site was the head and neck (8 cases); six of the latter sites were classified as cranial parameningeal (Table). Other primary sites were genitourinary (n=3), extremity (n=3), pelvis (n=3), and trunk (n=2). Tumour size was greater than 5 cm in diameter in 47% of cohort, and over two thirds had evidence of local tissue invasion (T2) at diagnosis. Thirty-two percent did not manifest regional lymph nodes, 47% had manifested regional lymph node involvement and in 21% the lymph node status was unknown (Table). Thirteen (68%) of 19 patients had embryonal and six had alveolar histology. Four, 3, 6, and 6 patients were classified as belonging to IRS stage I, II, III, and IV groups, respectively. The distant metastatic sites of the six stage IV cases were the lung

TABLE. Demographic and clinical features, treatment regimens, and outcomes of the rhabdomyosarcoma patients

Patient No.	Age (yrs)	Sex	Site*	Histology†	IRS stage‡	IRS group
1	17.2	F	GU	1	IV (T2b N1 M1)	4
2	17.4	M	GU	2	I (T1a N0 M0)	1
3	0.5	M	Trunk	1	IV (T2b N1 M1)	4
4	12.2	F	PM	2	III (T2b N1 M0)	3
5	0.6	F	H&N	2	I (T1a N0 M0)	3
6	10.0	M	Pelvis	1	IV (T2b N1 M1)	4
7	1.3	M	Trunk	1	II (T1a N0 M0)	2
8	3.0	F	PM	1	IV (T2a N0 M1)	4
9	2.2	F	PM	1	III (T2a N1 M0)	3
10	1.8	F	Extremity	1	II (T2a Nx M0)	2
11	8.6	M	PM	1	III (T2b N0 M0)	3
12	5.7	F	Pelvis	1	III (T2b Nx M0)	3
13	9.7	F	Extremity	2	IV (T1b Nx M1)	4
14	4.3	M	PM	1	III (T2b N1 M0)	3
15	16.0	M	Pelvis	2	IV (T2 N1 M1)	4
16	6.8	M	GU	1	I (T2b N0 M0)	1
17	9.3	F	H&N	1	I (T2a N1 M0)	3
18	2.7	F	Extremity	2	III (T2a N1 M0)	3
19	3.6	F	PM	1	II (T2a Nx M0)	3

* Primary sites: GU=genitourinary (non-bladder/prostate); H&N=head and neck, non-parameningeal; PM=parameningeal
† Histology: 1=embryonal; 2=alveolar
‡ IRS denotes Intergroup Rhabdomyosarcoma Study
§ Chemotherapy protocol: 1=IRS-IV; 2=IRS-V; 3=International Society of Paediatric Oncology Malignant Mesenchymal Tumour (SIOP MMT)–89 protocol
‖ Radiotherapy (RT) type: 1=conventional RT; 2=intensity-modulated RT; 3=3D-conformal RT; *=including right thigh 50.4 Gy, boost local 32 Gy, right lung 18 Gy; ND=not done; NA=information not available; D0=at diagnosis
¶ Surgery: 1=complete resection; 2=partial resection; ND=not done; NA=information not available; D0=at diagnosis
** ABMT denotes autologous bone marrow transplantation
†† Status: DOD=died of disease, NED=no evidence of disease, DOI=died of infection, AWD=alive with disease

(50%), bone (33%), and lymph nodes (33%). Median follow-up duration was 3.4 (range, 0.2-16.7) years.

Treatment

Multimodality treatment comprising chemotherapy, surgery, and RT was used for our RMS patients; the majority of whom received full-dose chemotherapy as specified by the corresponding chemotherapy protocol (mainly IRS-IV regimen, Table), except that the dose was reduced (to 50-75%) in two infants. According to the IRS-IV protocol, we adopted the standard treatment arm—VA (vincristine and actinomycin D) for stage I group 1, stage I group 2 orbit, stage I group 1 or 2 paratesticular tumour; and VAC (vincristine, actinomycin D, and cyclophosphamide) for all other categories of non-metastatic RMS. Granulocyte–colony stimulating factor was not given prophylactically following each cycle of VAC, but was added as rescue therapy (5 μg/kg/day) when the patient developed neutropenic fever. Significant toxicity such as severe oral mucositis was encountered, particularly during concurrent RT and chemotherapy. Interruption and delay to the scheduled chemotherapy with subsequent reduction of the dose of actinomycin D was deemed necessary in three (16%) of the patients with persistent mucositis (NCI-CTC grade 4). Vincristine was discontinued in two patients who developed severe peripheral neuropathy (NCI-CTC grade 4).

Only five of 19 patients had surgical resection of the primary tumour at diagnosis; two (11%) achieved complete resection (IRS group 1) whilst two (11%) had microscopic residual disease (IRS group 2). The majority had a biopsy only at diagnosis; nine (47%) were in group 3, and six (32%) in group 4. Overall, 10 (53%) patients underwent surgical resection of the primary tumour, and complete resection was achieved in seven, whereas gross residual disease remained in three (Table). Surgical resection was not feasible in five of the six children with cranial parameningeal disease (Table).

Treatment regimen							Overall survival (yrs)	Event-free survival (yrs)	Status††
Chemotherapy§	Radiotherapy‖			Surgery¶		ABMT**			
	Type	Timing (weeks)	Dose (Gy)	Type	Timing (weeks)				
1	3	16	54	ND	-	-	0.9	0.6	DOD
1	ND	-	-	1	D0	-	5.7	5.7	NED
1	3	36	50.4	2	D0	Yes	3.6	2.1	DOD
1	3	7	50.4	ND	-	-	2.4	1.2	DOD
1	ND	-	-	1	10	-	3.4	3.4	NED
1	1	D0	24	ND	-	-	0.2	0.2	DOD
1	1	9	41.4	1	D0	-	9.6	9.6	NED
1	2	3	50.4	ND	-	-	0.7	0.7	DOI
1	3	9	50.4	ND	-	-	6.1	3.7	NED
1	1	10	50.4	1	D0	-	3.4	2.4	DOD
1	2	3	50	ND	-	-	4.9	4.1	AWD
2	1	16	36	2	10	-	1.2	1.2	NED
1	1	NA	*	1	NA	-	16.7	16.7	NED
1	3	10	50.4	ND	-	-	6.1	6.1	NED
1	1	NA	54	ND	-	Yes	1.8	1.8	DOD
1	ND	-	-	1	D0	-	7.5	7.5	NED
1	1	10	50.4	ND	-	-	1.4	1.4	DOI
1	1	23	41.4	1	20	Yes	5.8	1.1	NED
3	1	NA	NA	2	NA	Yes	3.1	2.2	DOD

Sixteen (84%) of the 19 patients received RT; the exceptions being two with stage I group 1 disease and an infant who had delayed complete resection of a right nasal ala tumour (Table). Over the entire study period, three types of RT were administered—9 (56%) of 16 patients received conventional RT, two received intensity-modulated RT, and five were given three-dimensional conformal RT. Most patients received total RT dosages of between 41.4 and 50.4 Gy. Radiotherapy was usually administered after the induction phase of chemotherapy, at about 9 and 16 weeks of treatment. Cranial parameningeal cases that showed evidence of either skull base erosion, intracranial extension or cranial nerve palsy commenced RT within the first few weeks of treatment concurrent with chemotherapy (Fig 1). Four patients, including one with metastases and three relapsed patients, underwent autologous bone marrow transplantation; only one of whom remains alive.

Survival and outcome

Five-year OS and EFS rates of the whole cohort of patients were 49% (95% confidence interval [CI], 26-73%) and 32% (95% CI, 10-55%), respectively (Fig 2). Patients with non-metastatic tumours (IRS group 1-3) had much better outcomes than the others (IRS group 4). The 5-year OS rate was 66% (95% CI, 39-93%) in non-metastatic cases, compared to 17% (95% CI, 0-46%) in metastatic cases (Fig 3a). Five-year OS rate for patients less than 10 years old was 60% (95% CI, 33-87%) compared to 20% (95% CI, 0-55%) for those who were older (Fig 3b). There was no difference in survival between those with embryonal and alveolar histology tumours. The series of patients was too small to allow meaningful analysis of the impact of potential prognostic factors, such as primary tumour site, IRS staging and grouping.

There were 11 treatment failures in 19 patients—disease relapse (n=7), death due to severe infection (n=2), second malignant neoplasm (n=2).

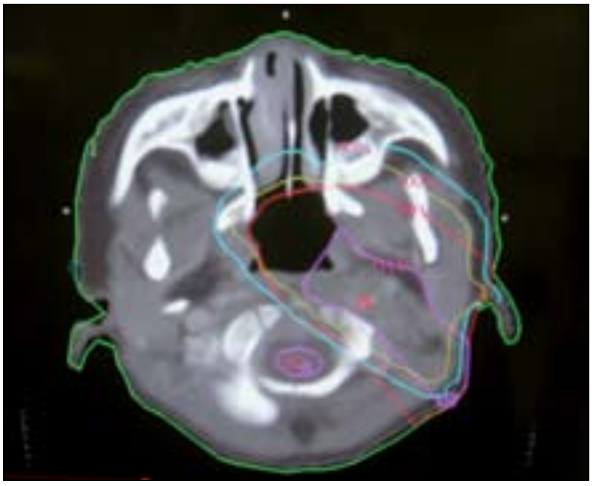

FIG 1a. Radiotherapy planning for a cranial parameningeal (parapharyngeal) rhabdomyosarcoma in a 3-year-old patient

The magenta line outlined the gross tumour volume (GTV), the red line outlined the planning target volume (PTV), the yellow and cyan lines represented the 100% and 90% isodoses, respectively; SC denotes spinal cord

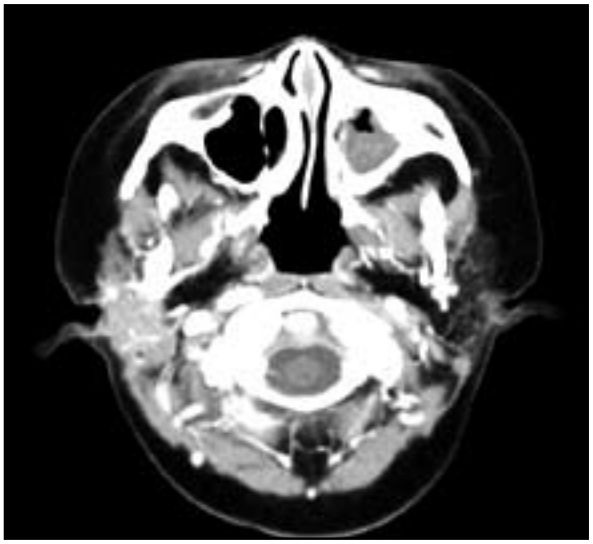

FIG 1b. Complete remission of the tumour after chemotherapy and radiotherapy; no surgical resection was performed

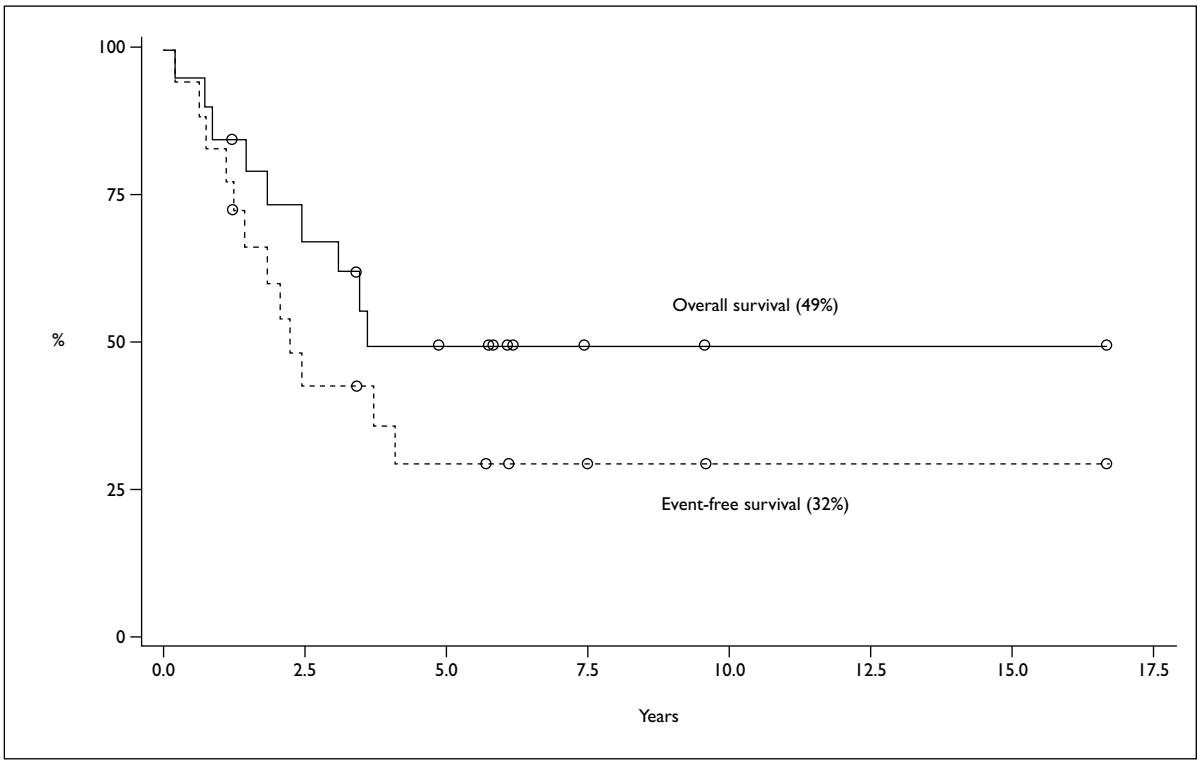

FIG 2. Overall and event-free survival of the 19 rhabdomyosarcoma patients

Relapse was local in one (14%) patient, regional in two (29%) and combined local and distant relapse in four (57%). The median time interval from diagnosis to relapse was 25 months. The five relapsed patients died. One patient was alive with progressive disease, and another who underwent an autologous bone marrow transplant survived, with no evidence of disease.

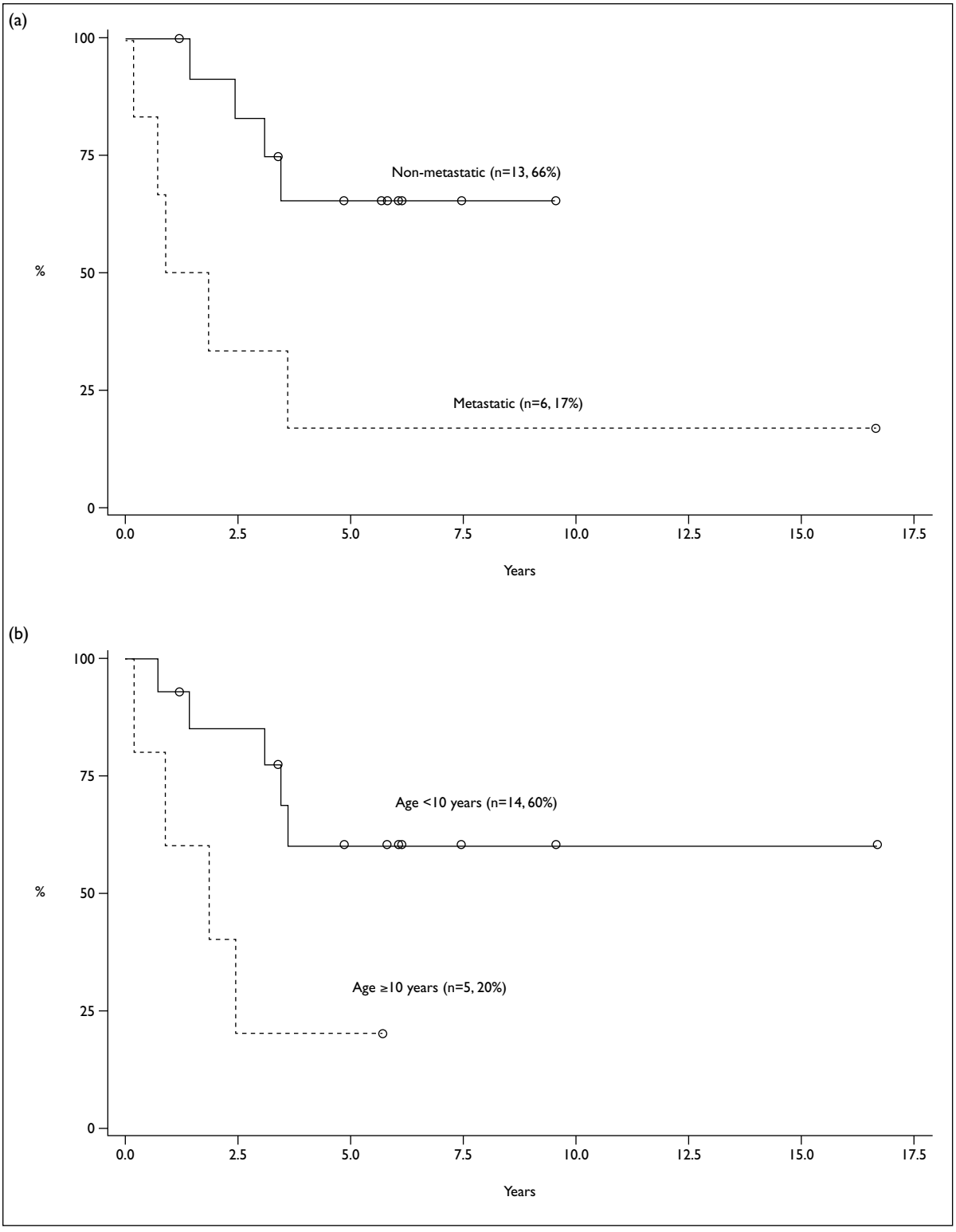

FIG 3. (a) Survival of non-metastatic and metastatic rhabdomyosarcoma. (b) Impact of age on survival of rhabdomyosarcoma

Toxicity data

Significant toxicity was encountered with the VAC treatment regimen. According to the NCI-CTC version 2.0,[14] 16 (86%) patients experienced myelosuppression with five (26%) reaching grade 4 severity. Infections such as neutropenic fever occurred in almost every patient; multiple episodes were frequently encountered by individual patients. Severe septicaemia associated with profound neutropenia developed in two patients resulting in their death; one during the IRS-IV treatment regimen and one after the last cycle of VAC cycle

before recovery from myelosuppression, three (16%) had severe (CTC grade 4) mucositis, four (21%) had moderate-to-severe vincristine-induced neuropathy (CTC grade 3 or 4), and four (21%) had renal toxicity. Two (11%) patients developed second neoplasms (both undifferentiated sarcomas) at 44 and 49 months after initial diagnosis of RMS.

Discussion

The primary aims of this study were to review the Hong Kong experience of treating RMS, a rare group of childhood tumours, and identify potential areas for improved management. The 5-year OS and EFS rates in this RMS cohort in Chinese children treated in a single institution were 49% and 32%, respectively. The Kaplan-Meier curve for EFS indicated that most relapses occurred within 2.5 years of diagnosis. The late events were second malignant neoplasms occurring 3.7 and 4.1 years post-diagnosis. Survival outcome appeared inferior to those reported by IRSG and in other international studies[3,8,11,12]; the outcomes of our patients belonging to different IRS groups were examined to identify possible reasons.

The higher percentage (32%) of patients with metastatic RMS (IRS group 4) in our cohort compared to the average of 15% reported in international studies[8,15,16] was the most likely factor accounting for our inferior OS. A marked difference in survival was observed when the patients were separated according to metastatic (17%) and non-metastatic (66%) status (Fig 3a), since metastatic RMS confers poor survival worldwide. The 3-year OS and EFS rates were 39% and 25%, respectively in the 127 patients with metastatic RMS treated by the IRS-IV study.[17] In the same study, a subgroup of patients with embryonal histology and two or fewer metastatic sites had higher OS (47%) and EFS (40%) rates.[17] A retrospective review of 19 patients with metastatic RMS treated at the Hospital for Sick Children in Toronto over a 10-year period also identified a subset of patients (<10 years old with embryonal histology and metastases confined to the lungs) with a much more favourable prognosis.[18] The 5-year OS and EFS rates of 174 metastatic RMS patients participating in two consecutive European studies (MMT4-89 and MMT4-91) were 24% and 20%, respectively. However, those with fewer than two unfavourable factors (unfavourable site and age, as well as bone or bone marrow metastases) had respective 5-year EFS and OS rates of 40% and 47%, compared to less than 10% survival in the remainder.[19] In our series, one of the six IRS group 4 patients (case 13, Table) presenting at the age of 9 years with alveolar RMS of an extremity and pulmonary metastases was the only long-term survivor. Other patients had multiple adverse factors such as unfavourable age (>10 years or <1 year) or distant metastases at multiple sites.

Among the nine IRS group 3 patients (unresectable tumours or those with incomplete resection), all except two were in the head and neck region, of which five were cranial parameningeal. Among the five patients with parameningeal tumours, two died of the disease whilst three achieved complete remission. However, only one remained in continuous complete remission; the other two developed a second cancer at or near the radiation field. One patient was salvaged with chemotherapy and complete resection of the second tumour, whilst the other had progressive disease. Importantly, non-metastatic parameningeal tumours can be treated successfully by combined chemotherapy and radiation to the initial tumour volume, without the need for aggressive surgical resection.[20,21] Again, our results were inferior to the 5-year OS rate of 73% (95% CI, 70-77%) for 611 patients with localised parameningeal tumours treated in the IRS II-IV studies.[20] Improvement in supportive care as well as advances in RT techniques[22] (accurately defining the tumour target volume with fusion of magnetic resonance images) are important in the treatment of this group of patients.

Most treatment failures in our patients were in disease relapses at local, regional, or distant sites. In both IRS-III and IRS-IV trials, local failure risk exceeded the risk of distant metastases as a first failure event.[3,9] The IRS-V study explored the role of surgery in reducing local failures after induction chemotherapy (12 weeks for most group 3 patients).[13] Postoperative RT is required but the dose is determined by resection margin status. In our series, complete surgical resection was mainly achieved in IRS group 1 and 2 patients, who enjoyed excellent survival. The feasibility of surgical resection of tumours after induction chemotherapy, while also preserving form and function, should always be explored rigorously in individual patients.

Age has been shown to be an important prognostic factor for certain subgroups of RMS.[23] A significant difference in survival between patients aged less than 10 years and those who were older (Fig 3b) was noted. However, arguably older patients in our series had more advanced and invasive disease. Histological subtype has been consistently shown to be one of the most important prognostic factors for RMS; alveolar tumours generally have worse survival outcomes.[23] There was no survival difference between patients with embryonal and alveolar RMS in our cohort of patients, very likely due to the small numbers and the advanced clinical grouping (3 or 4) of the majority (75%) with embryonal histology.

Significant treatment-related toxicities were observed in the 19 patients of our series, treated mainly according to the IRS-IV protocol. Intensified therapy used in IRS-IV resulted in myelosuppression

(>90%) with subsequent episodes of severe infections (55%) and death (1%), severe renal toxicity (2%) and second cancers in 10 (1.1%) of 883 patients.[3] We observed frequent occurrence of myelosuppression (86%), severe mucositis (16%), renal toxicity (21%), and severe vincristine-induced neuropathy (21%). Two patients died of severe septicaemia. In two patients with parameningeal tumours, following relatively short latency periods, second malignant neoplasms (both undifferentiated sarcomas) developed within or near the radiation field. The latter were possibly due to the use of alkylating agents and RT. Development of appropriate supportive care is essential to minimise complications of this treatment regimen.

In conclusion, this retrospective review of a series of childhood RMS patients and experience in treating this cancer in Hong Kong identified potential aspects of management deserving improvement. These included post-chemotherapy supportive care, surgical resection of residual tumours, and usage of contemporary RT strategies, all of which should be targeted for continual development in the management of RMS.

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