Results of RS-99 protocol for childhood solid tumors

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Background: **Little was known about the therapeutic result of rhabdomyosarcomas (RMSs) and other malignant tumors until the end of the last century in China. Very few prospective clinical research results have been reported. We designed a RS-99 protocol under close cooperation of a multidisciplinary team including surgeons, radiologists, pathologists, and pediatric oncologists at Shanghai Children's Medical Center. This study aimed to improve the prognosis of childhood solid tumors and analyze the results of different tumors with the same protocol, including RMSs, the Ewing sarcoma family of tumors (ESFTs), and ex-cranial germ cell tumors (GCTs).**

Methods: **Sixty-six patients with malignant solid tumors [RMS (*n*=30), GCT (*n*=22), and ESFT (*n*=14)] were enrolled on the RS-99 protocol from October 1998 to October 2006. They were 34 girls and 32 boys aged 9 to 194 months. The protocol involved surgery, radiotherapy and chemotherapy which included VCP (vincristine, cis-diaminedichloroplatinum, and cyclophosphamide) and IEV (etoposide, vincristine and ifosfamide) for the low-risk group, AVCP (adriamycin, vincristine, cis-diaminedichloroplatinum, and cyclophosphamide) and IEV for the intermediate-risk group and high-risk group. Peripheral blood stem cell transplantation was suggested for the high-risk group. Radiotherapy was only given for RMS and ESFT. Differences in survival between the groups were determined by comparison of entire survival curves and tested by the Kaplan-Meier method and the log-rank tests.**

Results: **The 5-year event-free survival (EFS) for the whole group (RMS, ESFT and GCT) was 60%. The 5-year EFS for children with RMS was 35% (95% CI 16-54), GCT was 79% (95% CI 70-88) and ESFT was 72% (95% CI 58-86). The 5-year EFS showed that the patients with RMS in the retroperitoneum-pelvis did not have a better result than those with tumors in other sites (*P*=0.604). The histological classification of RMS exerted prognostic influence on the estimated 5-year EFS (*P*=0.04). Tumor stage and risk group were also contributive to prognosis (*P*=0.008). For GCT patients, the primary sites of tumors and their histological classification did not influence the therapeutic result (*P*=0.814). The 5-year EFS was 100% in stage I and II versus 62% in stage III and IV patients (*P*=0.02). Because of the small number of patients, we did not analyze the prognostic factors for patients with ESFT. No organ failure or functional impairment occurred in the patients enrolled in the RS-99 protocol. One ESFT patient developed a second cancer.**

Conclusions: **The RS-99 protocol is well tolerated and is reasonable for the 3 different tumors. Risk-based grouping protocol design is needed and the protocol for high risk RMS should be revised.**

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Key words: **children;**
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Introduction

Soft tissue sarcomas (STSs) are a heterogeneous group of malignant tumors, which make up approximately 7% of all childhood tumors and represent the fourth most common group of malignancies in children of less than 16 years old after leukemia, central nervous system tumor and neuroblastoma.[1] Rhabdomyosarcomas (RMSs), tumors of striated muscle, account for more than one-half of all cases of STS in children.[2] Patients are usually treated with a multi-modality therapeutic approach including surgery, chemotherapy, and radiotherapy, based on the ongoing protocol at the time of diagnosis. Since

the Intergroup Rhabdomyosarcoma Study Committee (IRS) was established in 1972 for performing large randomized trials to foster the field forward, four consecutive trials have been designed and conducted; the cure rate increasing from 25% in 1970 to 75% in 1997.[3,4]

Germ-cell tumor (GCT) is different from STS, accounting for 3% to 4% of childhood malignancies (<15 years old). Localized tumor has a good prognosis, but for patients with an advanced form of the disease, it still requires more aggressive chemotherapy. The 5-year survival rate of these patients following standard-dose chemotherapy is only about 45%.[5]

The Ewing sarcoma family of tumors (ESFTs) [extra skeletal Ewing sarcoma (EES) and peripheral neuroectodermal tumor (PNET)] represent the second most frequent histological group of soft tissue sarcomas in children and adolescents (approximately 8% to 10% of all STS). Current treatment strategies in localized Ewing tumor (ET) yield a 5-year disease-free survival (DFS) rate of 50%-70%. In contrast, the metastatic disease at diagnosis is associated with a 5-year survival rate of below 30%.[6]

According to the experience of IRS, we designed the RS-99 protocol under close cooperation within a multidisciplinary team including surgeons, radiologists, pathologists, and pediatric oncologists in Shanghai Children's Medical Center. The diagnosis and staging criteria, surgery, chemotherapy, and radiation therapy were standardized in the RS-99 protocol. The rarity of each histotype prevented the performance of clinical trials on a single tumor type. Both ESFT and RMS have similar sensitivity to a single agent, including vincristine, doxorubicin, cyclophosphamide, actinomycin D, ifosfamide, and etoposide. Various reports have shown that those agents are also sensitive for GCT. Therefore, patients with RMS, ESFT, and GCT were treated with the same therapeutic protocol, RS-99, in this study. However, primary lesions of GCT limited in the testis were excluded because of their good prognosis.[7]

Methods

Eligibility was restricted to patients receiving one of the diagnoses as follows: RMS, ex-cranial ESFT or GCT at our hospital between October 1998 and October 2006. Patients were included in this cohort if they were less than 21 years old with either resectable, incompletely resected, or metastatic tumor at the time of presentation. The patients who had undergone chemotherapy were excluded. Histopathological examination, which was performed at local centers, had to be reviewed by our pathologists before therapy. The study population included patients with RMS (n=30), GCT (n=22), and ESFT (n=14). The extent of the disease was determined by clinical examination, standard X-rays, and a computed tomography (CT) scan or magnetic resonance imaging (MRI). Ultrasound examination was performed repeatedly during chemotherapy for evaluating responses of any intra-abdominal or pelvic tumors. Cerebrospinal fluid examination was required for all parameningeal tumors. Chest un-enhanced CT and technetium bone scans with MRI for abnormal bone scan sites were required to detect distant metastases. Bone marrow aspiration at single site was performed in all patients.

ESFT and GCT patients were staged according to the clinical tumor node-metastases (TNM) classification[8,9] and RMS patients were staged according to the IRS Staging Classification.[3] The patients were treated according to various treatment strategies based on their grouping which depended on their pretreatment stage, tumor site and pathological classification. Three levels of the risk group were identified based on stage, site, and histological classification in the RS-99 protocol (Table 1). The Institutional Ethic Review Board approved the study, and the parents or guardians of the patients signed a consent form.

Therapy

Surgery was encouraged when complete tumor removal was possible without sacrificing organ function. However, this was not always feasible at presentation because of the large size and infiltration of neighboring tissues or organs. Patients received multiple-agent chemotherapy within 7 days after surgery. The overall treatment schedule, details of chemotherapy, and time arrangement are shown in Table 2. Drug doses were reduced by 25% for infants younger than 1 year to avoid excessive toxicity. The course of the treatment lasted for 21 days or when the absolute neutrophil count (ANC) was greater than 1000/μL and the platelet count

Table 1. Clinical grouping system used for solid malignancies (RMS, GCT and ESFT)

Low-risk group	Non-alveolar RMS at stage I
	GCT at stage I except for primary testis lesions
	ESFT at stage I
Intermediate-risk group	Alveolar RMS at stage I, RMS at stage II, non-alveolar RMS at stage III
	GCT and ESFT at stage II and III
High-risk group	Alveolar RMS at stage III, RMS at stage IV
	GCT and ESFT at stage IV

RMS: rhabdomyosarcoma; GCT: germ cell tumor; ESFT: Ewing sarcoma family of tumor.

Table 2. Treatment plans for solid malignancies (RMS, GCT and ESFT)

Group	Week	0	3	6	9	12	15	18	21		22	25	28	31	34	37	
LR	Surgery	V	I	V	I	V	I		Regional radiotherapy	Evaluation							
		C	E	C	E	C	E										
		P	V	P	V	P	V										
MR/HR	Surgery or biopsy	A		A		A		Radiotherapy	Second operation	Evaluation							PBSCT
		V	I	V	I	V	I				V	D	V	D	V	D	
		C	E*	C	E*	C	E*				C	E	C	E	C	E	
		P	V	P	V	P	V				P	V	P	V	P	V	

V: vincristine 1.5 mg/m^2, days 0, 7; C: cyclophosphamide 300 mg/m^2, days 1-3; P: cis-diaminedichloroplatinum 90 mg/m^2, days 0; I: ifosfamide 1.5 g/m^2 per day, days 1–5; E: etoposide 100 mg/m^2 per day, days 1-3; A: adriamycin 30 mg/m^2, days 1, 8; E*: etoposide 100 mg/m^2 per day, days 1–5; D: dactinomycin 0.012 mg/kg per day, days 1–5. PBSCT: peripheral blood stem cell transplantation (only for HR). LR if resected completely, only 4 courses.

was greater than 75 000/μL.

The low-risk (LR) group received 4-6 courses of alternating cycles of VCP composed of vincristine (VCR), cis-diaminedichloroplatinum (CDDP), cyclophosphamide (CTX) and IEV composed of etoposide (VP-16), VCR and ifosfamide (Ifos). Patients aged 3 years and above with RMS and ESFT were considered for local radiation therapy after the 4-6 courses of chemotherapy. The prescribed dose of radiation was 4500 cGy-5500 cGy in 200 cGy daily, 5 days a week. The radiation fields included the initial tumor bed plus 2-3 cm margins. No radiotherapy was administered for GCT patients.

The intermediate-risk (MR) group received 6 courses of alternating cycles of AVCP composed of adriamycin (ADR), VCR, CDDP, CTX and IEV composed of VP-16, VCR and Ifos. Local radiation therapy was delivered after course 6. After radiotherapy, the dose of chemotherapy was reduced. If the tumor could not be removed at presentation, delayed or second surgery was arranged during courses 3 to 6 when the tumor shrank and reached the status of complete or good gross resection. The chemotherapy was terminated with four more courses after reaching a complete response, but no more than 12 courses were given.

The high-risk (HR) group received chemotherapy, surgery, and radiotherapy identical to the intermediate group. A tumor resection was arranged after chemotherapy in almost all the patients. Usually, more courses were taken in this group than in the MR group because of later complete responses. High-dose chemotherapy with autologous peripheral blood stem cell transplantation (PBSCT) was encouraged at the end of therapy.

Statistical analysis

End points were disease progression, relapse, second malignancy, death, or last reported contact (if none of these other events occurred). Patients who did not experience the events of interest were censored at the time of their last follow-up. Overall survival (OS) and event-free survival (EFS) with 95% confidence intervals (95% CI) were estimated using actuarial life table methods. Differences in survival between various groups were evaluated by comparison of entire survival curves and tested according to the Kaplan-Meier method with the log-rank test. The Chi-square test was used to compare the frequency distribution of patient characteristics and to test for significant differences in response rates between the groups. Statistical analyses were conducted using SPSS13.0 software. *P* values were used for measurement of strength, and a *P* value less than 0.05 was considered statistically significant.

Results

Patient and clinical characteristics

From October 1998 to October 2006, 66 patients with newly diagnosed RMS, ESFT and GCT, who met all the eligibility criteria, were enrolled in the RS-99 protocol and their response and survival were analyzed.

Among the 64 patients, RMS was the most frequent histotype (30 patients, 49%). The median age of the patients was 42 months (range, 15 to 194 months). The mean follow-up of survivors was 27.4 months (range, 4 to 100 months). Clinical features of the patients are shown in Table 3. Twenty-seven percent (8/30) of the RMS patients only received chemotherapy, 23% (7/30) received gross resected surgery and chemotherapy but no radiotherapy, 27% (8/30) received chemotherapy, surgery and radiotherapy, 23% (7/30) received chemotherapy and radiotherapy for the initial tumor. Eight patients received PBSCT at the end of therapy.

Twenty-two GCT patients were enrolled in the RS-99 protocol. They were 8 males and 14 females, aged from 9 to 144 months at diagnosis with a median of 23.5 months, and a mean follow-up period of 27.7 months (range, 5 to 89 months).

Fourteen ESFT patients were enrolled in the study. Nine of them were male, aged from 19 to 140 months,

Table 3. Patient characteristics

	Rhabdomyosarcoma	Germ cell tumor (GCT)	Ewing sarcoma family of tumor
Number	30	22	14
Sex	15 male, 15 female	8 male, 14 female	9 male, 5 female
Age	15-194 mon (median 42)	9-144 mon (median 23.5)	19-140 mon (median 84.5)
Histology	20 Embryonal	15 YST	9 PNET
	8 Alveolar	4 Immature teratoma	5 Ewing sarcoma (ES)
	1 Pleomorphic	2 Dysgerminoma	
	1 Other	1 Granular cell tumor	
Primary site	10 Retroperitoneum-pelvic	11 Genital system	12 Trunk
	3 Head and neck	6 Sacroiliac	6 Chest wall (2 rib cage)
	3 Head and neck parameningeal	3 Mediastinum	2 Pelvis
	5 Extremity	2 Pelvis	2 Abdomen
	5 GU-BP		1 Thoracic spine
	1 GU-nonBP		1 Parameningeal
	2 Trunk		2 Extremity
	1 Cardiac muscle		2 Radius/ulna
Stage	4 IRS-I	5 GCT-I	8 Localized
	6 IRS-II	2 GCT-II	6 Metastatic
	8 IRS-III	10 GCT-III	
	12 IRS-IV	5 GCT-IV	
Risk	3 LR	6 LR	2 LR
	12 MR	10 MR	5 MR
	15 HR	6 HR	7 HR

YST: yolk sac tumor; IRS: Intergroup Rhabdomyosarcoma Study; LR: low-risk; MR: intermediate-risk; HR: high-risk; PNET: peripheral neuroectodermal tumor; GU-BP: genitourinary, including bladder-prostate.

with a median age of 84.5 months and a mean follow-up period of 43.7 months (range, 7 to 102 months) (Table 3). Six patients (42.8%) had remote metastasis disease at primary diagnosis. Fourteen percent of the patients were grouped into the LR group, 35.7% into the MR group and 50% into the HR group. Ten of the 14 (71%) patients received regional radiotherapy, and 5 received PBSCT at the end of therapy.

Treatment outcome

For the pooled data, the 5-year EFS for all the children with RMS, ESFT and GCT was 60%, but only 35% for the patients with RMS (95% CI: 16-54) [OS, 37% (95% CI: 21-53)], 79% for GCT (95% CI 70-88) [OS, 80% (95% CI: 70-90)] and 72% for ESFT (95% CI: 58-86) [OS, 88% (95% CI: 78-98)]. The difference among those three groups was not significant (P=0.3) (Fig. 1).

Seventy-seven percent of (23/30) RMS patients achieved complete response. Seven patients progressed after partial response, 3 of them are alive and in good partial responses, and 4 died. Five patients relapsed. Of the 22 patients with GCT, 19 (86%) achieved complete response and 1 of them relapsed. The remaining three patients were classified as no response. All the 14 patients with ESFT achieved complete response and 3 of them relapsed.

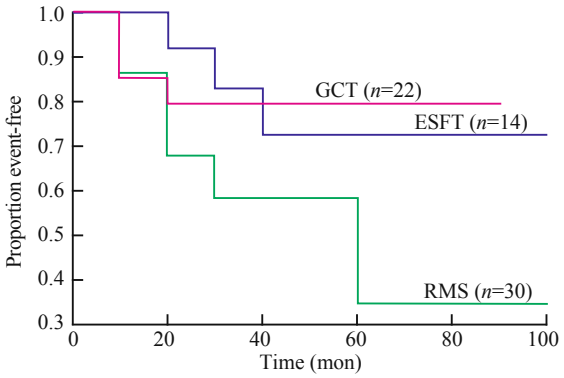

Fig. 1. Kaplan-Meier survival curve comparing event-free survival of patients with RMS (35%), GCT (79%), and ESFT (72%) (P=0.3).

Prognostic factors of RMS

The most common primary site was retroperitoneum-pelvis (33.3%), the outcomes were not significantly different from those in other sites (P=0.604). Histologic type exerted prognostic influence, with an estimated 5-year EFS rate of 54% for patients with embryonal RMS, and 27% for those with alveolar RMS (P=0.04, Fig. 2). Tumor stage showed prognostic importance (5-year EFS rate: stage I+II, 100%; stage III, 62%; stage IV, 20%; P=0.008; Fig. 3). When prognosis was analyzed by groups, patients with tumors in the LR or MR group had a better outcome than those in the HR

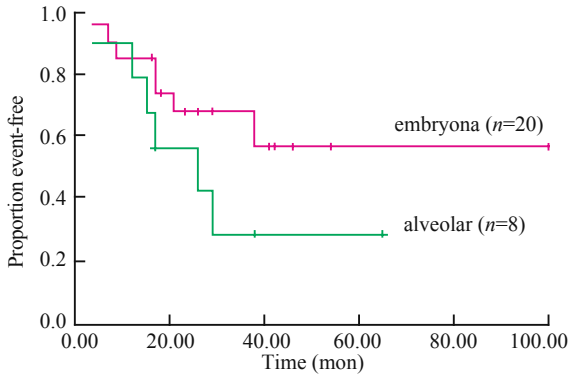

Fig. 2. Kaplan-Meier survival curve comparing event-free survival of patients with RMS according to histological classification (embryonal, alveolar) (P<0.05).

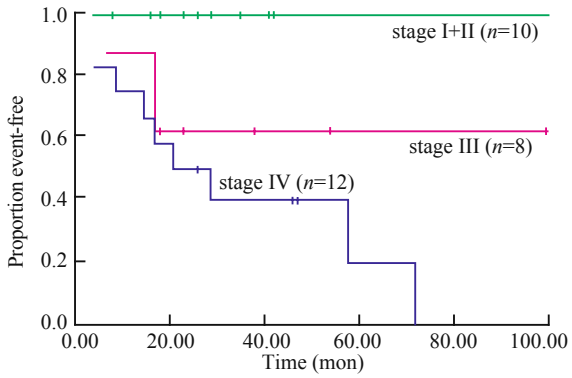

Fig. 3. Kaplan-Meier survival curve comparing event-free survival of patients with RMS according to stages (P<0.01).

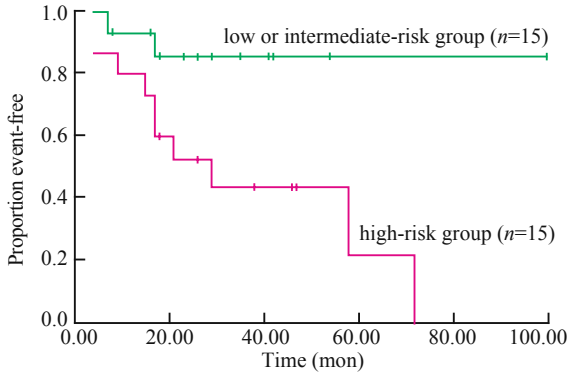

Fig. 4. Kaplan-Meier survival curve comparing event-free survival of patients with RMS according to risk groups (P=0.01).

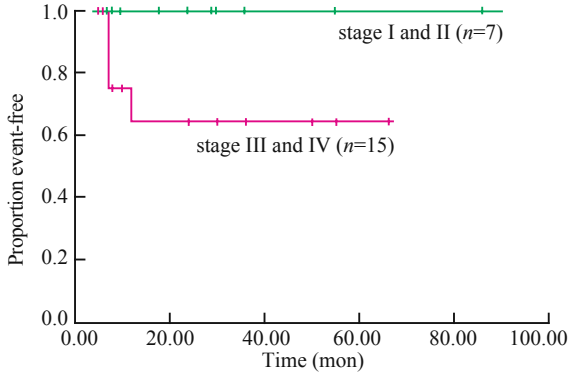

Fig. 5. Kaplan-Meier survival curve comparing event-free survival of patients with GCT according to stages (P=0.02).

group (5-year EFS: LR or MR group, 86%; HR group, 22%; P=0.01; Fig. 4).

Prognostic factors for GCT

The 5-year EFS for patients with tumors in the genital system (50%), the most predominant primary sites, was not significantly better than that of patients with tumors in other sites (88% vs. 68%, P=0.352). Histologically, yolk sac tumor exerted prognostic effect on EFS, compared with immature teratoma, dysgerminoma and granular cell tumor, but the difference was not significant (5-year EFS, 83% vs. 76%, P=0.814). The 5-year EFS was higher in stage I and II (100%) than in stage III and IV (62%) (P=0.02) (Fig. 5). Prognosis of patients in the LR group or MR group was better than that of those in the HR group, but the difference was not significant (5-year EFS: LR or MR group, 87%; HR group, 72%; P=0.533).

Prognostic factors for ESFT

We did not evaluate tumor primary sites as outcome predictor because of the small number of patients. Three relapsed patients all had trunk primary sites with advanced local extensive tumors. There was no correlation between the histological subtype and outcome (P=0.984). The prognosis of patients in the low-risk group or intermediate-risk group was better than that of those in the high-risk group, but the difference was not significant (5-year EFS: low or intermediate-risk group, 75%; high-risk group, 67%; P=0.564).

Toxicity

No organ failure or functional impairment from chemotherapy occurred in the patients enrolled in the RS-99 protocol. Most (90%) of the patients experienced myelosuppression. Severe pneumonia or septicemia was observed in 10% of the patients. The levels of blood urea nitrogen and creatinine were temporarily increased in only 2% of the patients. Acute gastrointestinal toxicity (nausea and vomiting) was seen frequently. One patient with ESFT developed a second cancer, acute premyeloid leukemia, 3 years after diagnosis. He received regional radiotherapy of 5400 cGy at spinal columns and chemotherapy.

Discussion

Patients with local diseases can expect an extremely good prognosis whereas those with metastatic or locally advanced disease continue to have a poor prognosis and require more intensive therapy. Currently, the introduction of multimodality treatment has dramatically improved the prognosis of patients with ESFT and RMS.[10,11] Because empiric radiotherapy may result in an unnecessary overtreatment, radiotherapy was not recommended for GCT patients in this study.

The new European Pediatric Soft Tissue Sarcoma Study Group (EPSSG) developed a new protocol tailored specifically to non-rhabdomyosarcomas soft tissue sarcoma (NRSTS). Moreover, most of the experience gained in the treatment of pediatric NRSTS has been based on principles deriving from the management of RMS.[12] Both ESFT and RMS have similar sensitivity to single agents including vincristine, doxorubicin, cyclophosphamide, actinomycin D, ifosfamide, and etoposide.[13] These agents also proved efficacious in treating GCT. In our study, patients with different tumors including RMS, ESFT, and GCT were treated with the same multi-modality therapeutic protocol RS-99. The results revealed a 5-year EFS rate of 35% and an OS rate of 36% for RSM, 79% (OS, 80%) for GCT, and 72% (OS, 88%) for ESFT. The results indicate that this protocol is effective for both GCT and ESFT, and is comparable to those disease specified protocols. Except for high-risk RMS, others obtained reasonable good results with the same protocol. Hence it may be beneficial to optimize the agents combination and chemotherapeutic dosage, particularly for patients with advanced stages RMS.

Accurate tumor staging is of paramount importance because it helps to stratify treatment intensity accordingly, avoiding over or under treatment of patients and keeping the treatment effective and safe.[14] The European metastatic rhabdomyosarcoma studies MMT-89 and MMT-91 reached a 5-year EFS rate of 20%-30%.[15] Unfavorable prognostic factors for OS and EFS include primary tumor in the parameningeal region, localization in an extremity, age younger than 1 year and older than 10 years, bone or bone marrow metastases, and multiple metastases. Multivariate analysis revealed two groups of patients: patients with fewer than two unfavorable factors (5-year EFS 40% and OS 47%) and those with two or more unfavorable factors (5-year EFS 7.5% and OS 9%) could be identified.[16]

Before the advent of multimodal therapy, children with GCT can expect poor outcomes. The Einhorn regimen dramatically improved the outcome of adults with testicular GCT and quickly became the standard of care for adults with testicular tumors.[17] As Modak et al reported,[18] the estimated 4-year OS and EFS rates for patients with relapsed or progressive cranial GCT after high-dose chemotherapy and autologous stem-cell treatment were 57% and 52%, respectively. We conclude that cisplatin-based combination chemotherapy can improve the outcome of patients with GCT. The RMS-like regimen was used in this study, and the result is reasonably good with a 5-year EFS rate of 100% in stage I and II, and 62% in stage III and IV. It is suggested not only cisplatin-based PEB (cisplatin, etoposide and bleomycin) regimen works for GCT, but also RMB-like regimen.

For children with ESFT, wide surgical resection leads to a substantially better outcome than no surgical procedure. A retrospective analysis of patients with tumors localized in the extremities showed that the 5-year EFS was substantially better in patients treated by surgery than in those treated by radiotherapy (68% vs. 48%).[19] Chemotherapy cannot be omitted, and initially it consisted of vincristine, actinomycin D, and cyclophosphamide. Adding etoposide and ifosfamide proved to be effective in the treatment of ES.[20] The 5-year EFS rate up to 69% has been reported. Carboplatin as a second line agent in combined chemotherapy has resulted in a response rate of 26%.[21] Many treatment protocols recommend autologous stem cell supported high-dose chemotherapy for advanced stage disease, although the value of these procedures is still questioned.[22] The above mentioned factors were all considered in our RS-99 protocol.

In conclusion, RS-99 is safe. Except for high-risk RMS, it is reasonably good for the 3 different types of tumor with the same protocol but should be applied with a risk-based grouping protocol design. Further experience should be accumulated in undertaking the RS-99 protocol.

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Competing interest: No benefits in any form have been received or will be received from any commercial party related directly or indirectly to the subject of this article.

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References

1 Pappo AS, Shapiro DN, Crist WM, Maurer HM. Biology and therapy of pediatric rhabdomyosarcoma. J Clin Oncol 1995;13:2123-2139.

2 Raney RB, Anderson JR, Barr FG, Donaldson SS, Pappo AS, Qualman SJ, et al. Rhabdomyosarcoma and undifferentiated sarcoma in the first two decades of life: a selective review of the Intergroup Rhabdomyosarcoma Study Group experience and rationale for Intergroup Rhabdomyosarcoma Study V. J Pediatr Hematol Oncol 2001;23:215-220.
3 Pappo AS, Meza JL, Donaldson SS, Wharam MD, Wiener ES, Qualman SJ, et al. Treatment of localized nonorbital, nonparameningeal head and neck rhabdomyosarcoma: lessons learned from intergroup rhabdomyosarcoma studies III and IV. J Clin Oncol 2003;21:638-645.
4 Crist WM, Anderson JR, Meza JL, Fryer C, Raney RB, Ruymann FB, et al. Intergroup rhabdomyosarcoma study-IV: results for patients with nonmetastatic disease. J Clin Oncol 2001;19:3091-3102.
5 Lertkhachonsuk R, Manchana T, Termrungruanglert W, Vasuratna A, Sittisomwong T, Worasethsin P, et al. Outcome of recurrent and persistent disease of malignant ovarian germ cell tumor: a retrospective analysis at King Chulalongkorn Memorial Hospital. J Med Assoc Thail 2006;89:138-144.
6 Kolb EA, Kushner BH, Gorlick R, Laverdiere C, Healey JH, LaQuaglia MP, et al. Long-term event-free survival after intensive chemotherapy for Ewing's family of tumors in children and young adults. J Clin Oncol 2003;21:3423-3430.
7 Lu KH, Gershenson DM. Update on the management of ovarian germ cell tumors. J Reprod Med 2005;50:417-425.
8 Koscielniak E, Harms D, Henze G, Jürgens H, Gadner H, Herbst M, et al. Results of treatment for soft tissue sarcoma in childhood and adolescence: a final report of the German Cooperative Soft Tissue Sarcoma Study CWS-86. J Clin Oncol 1999;17:3706-3719.
9 Lawrence W Jr, Anderson JR, Gehan EA, Maurer H. Pretreatment TNM staging of childhood rhabdomyosarcoma: a report of the Intergroup Rhabdomyosarcoma Study Group. Cancer 1997;80:1165-1170.
10 Meyers PA, Krailo MD, Ladanyi M, Chan KW, Sailer SL, Dickman PS, et al. High-dose melphalan, etoposide, total-body irradiation, and autologous stemcell reconstitution as consolidation therapy for high-risk Ewing's sarcoma does not improve prognosis. J Clin Oncol 2001;19:2812-2820.
11 Duchesne GM, Stenning SP, Aass N, Mead GM, Fosså SD, Oliver RT, et al. Radiotherapy after chemotherapy for metastatic seminoma—a diminishing role. MRC Testicular Tumour Working Party. Eur J Cancer 1997;33:829-835.
12 Pizzo PA, Poplack DG. Principles and practice of pediatric oncology. Philadelphia: Lippincott Williams & Wilkins, 2002: 1017-1050.
13 Breitfeld PP, Lyden E, Raney RB, Teot LA, Wharam M, Lobe T, et al. Ifosfamide and etoposide are superior to vincristine and melphalan for pediatric metastatic rhabdomyosarcoma when administered with irradiation and combination chemotherapy: a report from the Intergroup Rhabdomyosarcoma Study Group. J Pediatr Hematol Oncol 2001;23:334-337.
14 Donaldson SS, Meza J, Breneman JC, Crist WM, Laurie F, Qualman SJ, et al. Results from the IRS-IV randomized trial of hyperfractionated radiotherapy in children with rhabdomyosarcoma—a report from the IRSG. Int J Radiat Oncol Biol Phys 2001;51:718-728.
15 Carli M, Colombatti R, Oberlin O, Bisogno G, Treuner J, Koscielniak E, et al. European intergroup studies (MMT4-89 and MMT4-91) on childhood metastatic rhabdomyosarcoma: final results and analysis of prognostic factors. J Clin Oncol 2004;22:4787-4794.
16 Flamant F, Rodary C, Rey A, Praquin MT, Sommelet D, Quintana E, et al. Treatment of non-metastatic rhabdomyosarcomas in childhood and adolescence: results of the second study of the International Society of Paediatric Oncology: MMT84. Eur J Cancer 1998;34:1050-1062.
17 George DW, Foster RS, Hromas RA, Einhorn LH. Update on late relapse of germ cell tumor: a clinical and molecular analysis. J Clin Oncol 2003;21:113-122.
18 Modak S, Gardner S, Dunkel IJ, Balmaceda C, Rosenblum MK, Miller DC, et al. Rosenblum. Thiotepa-based high-dose chemotherapy with autologous stem-cell rescue in patients with recurrent or progressive CNS germ cell tumors. J Clin Oncol 2004;22:1934-1943.
19 Bacci G, Ferrari S, Longhi A, Donati D, Barbieri E, Forni C, et al. Role of surgery in local treatment of Ewing's sarcoma of the extremities in patients undergoing adjuvant and neoadjuvant chemotherapy. Oncol Rep 2004;11:111-120.
20 Dunst J, Schuck A. Role of radiotherapy in Ewing tumors. Pediatr Blood Cancer 2004;42:465-470.
21 Grier HE, Krailo MD, Tarbell NJ, Link MP, Fryer CJ, Pritchard DJ, et al. Addition of ifosfamide and etoposide to standard chemotherapy for Ewing's sarcoma and primitive neuroectodermal tumor of bone. N Engl J Med 2003;348:694-701.
22 Meyers PA. High-dose therapy with autologous stem cell rescue for pediatric sarcomas. Curr Opin Oncol 2004;16:120-125.

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