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TURKISH EXPERIENCE WITH RHABDOMYOSARCOMA: AN ANALYSIS OF 255 PATIENTS FOR 20 YEARS*

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SUMMARY: Akyüz C, Sancak R, Büyükpamukçu N, Atahan L, Göğüş S, Kutluk T, Büyükpamukçu M. (Department of Pediatric Oncology, Hacettepe University Institute of Oncology, Ankara, Turkey). Turkish experience with rhabdomyosarcoma: an analysis of 255 patients for 20 years. Turk J Pediatr 1998; 40: 491-501.

Two hundred and fifty-five previously untreated patients (pts) with rhabdomyosarcoma (RMS) (age range 15 days to 17 years, median 5 years) were evaluated and treated in our institution. Head and neck primaries were seen in 125 patients (49%), abdomino-pelvic in 73 (29%), trunk and lung in 20 (5%) and extremity lesions in 37 (15%). The histology was: embryonal 137; alveolar 42; botryoid 18; pleomorphic 14. Forty-four patients could not be subclassified. The stage of the patients were as follows: 15 in stage I, 74 in stage II, 139 in stage III and 27 in stage IV, according to the IRS grouping system. Patients were treated with a combination of surgery and radiation to doses of 35-55 Gy according to the patient's age and stage. All the patients received chemotherapy according to VAC or pulse-VAC (before 1988) and modified AVAC (after 1988) protocol. Survival curves were calculated by the Kaplan-Meier method. The statistical significance of each variable was tested by the log-rank test. Overall survival was 42 percent at 10 years. Three important predictors for survival time were clinical group ($p<0.001$), age ($p<0.001$) and primary site ($p=0.005$). The best results involved clinical group I-II, age one to five years and orbital and genitourinary primary sites. An important predictor of survival time was also detected between those treated during the first ten years (1972-82) and last 10 years (1982-92), $p<0.005$. Of the 96 deaths, 37 were from progressive disease, 24 from infection, 4 during postoperative period (first 7 days), 18 from unknown causes and 13 from other causes. *Key words: rhabdomyosarcoma, childhood tumors, IRS grouping system, prognostic factors.*

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Rhabdomyosarcoma is the most common soft tissue sarcoma of childhood, representing four to eight percent of all malignant neoplasms in children under 15 years[1-3]. Rhabdomyosarcomas tend to disseminate early in the course of the disease. However, the survival rates of this tumor have increased from 30 to 70-80 percent during the last 20 years[4]. Early diagnostic methods, modern surgery, radiotherapy, multidrug chemotherapy and supportive care played an important role in this accomplishment. Nevertheless, more than half of those with newly diagnosed, unresectable (group III) or metastatic (group IV) tumors continue to die of their disease. The majority of all deaths among children with rhabdomyosarcoma occur in those who have an advanced disease at initial diagnosis. In this study, epidemiologic, clinical and histopathologic features, survival data, treatment results, and prognostic factors of childhood rhabdomyosarcoma are presented.

Material and Methods

Between January 1972 and December 1992, 255 previously untreated children under 18 years of age with rhabdomyosarcoma (RMS) were diagnosed, and followed up in our center. The cut off date for analysis in these 255 patients was December 1994. Data were obtained from patient charts and medical records. Pretreatment evaluation included history, physical examination, chest x-ray, and routine blood and biochemical tests. Further studies like bone marrow aspiration, cerebrospinal fluid examination and computerized tomography depended on the primary site. All patients were grouped according to the Intergroup Rhabdomyosarcoma Study III (IRS) grouping[5]. A biopsy/excision or debulking surgery was performed on all patients. All histopathologic specimens were reviewed by our pathologists. All patients were treated postoperatively using a Cobalt 60 teletherapy unit. The fields were determined according to the primary tumor size, surgical findings, pre-and postoperative radiological investigations. Primary tumor bed was covered with a safety margin of one-to-three cm depending on initial tumor size and applied surgery. Total dose delivered between 30-60 Gy given in 150-180 cGy increments, modified according to patient's age and site of the tumor. Attention was given to using multiple treatment fields whenever possible. Three different chemotherapeutic regimens were used depending on the year: VAC and pulse-VAC (before 1988) and modified AVAC (after 1988). The VAC and pulse-VAC consisted of sequential vincristine, actinomycin D and cyclophosphamide (orally for VAC, IV for pulse-VAC) whereas the modified AVAC protocol consisted of sequential vincristine, cyclophosphamide, adriamycin, and actinomycin D.

Prognosis was defined on the basis of survival. Survival curves were calculated by the Kaplan-Meier method[6]. Groups were compared with respect to time to

local failure and survival duration using the log-rank test[7]. Variables investigated included age, sex, race, histology, primary site, and extent of tumor at initial presentation.

Results

During the period of January 1972-December 1992, 6,505 patients with malignant tumors were seen in Hacettepe Children's Hospital. Two hundred and fifty-five (4%) of these patients had rhabdomyosarcomas. The median age was five years (range 15 days-17 years). The boy to girl ratio was 158/97 (1.6/1). Demographic features and prognostic factors were analyzed. The age and sex, primary site at presentation, histology of disease, clinical group distribution and outcome of patients are summarized in Tables I-V, respectively. A total of 146 (57%) patients were under five years of age. Table IV shows stages of the patients. Almost 65 percent of patients had primary nonresectable tumors or metastatic disease (stage III-IV) at presentation. The histological subgroups of forty-four patients were not verified. All of the unclassified rhabdomyosarcoma slides were referred from some other hospital; therefore, our pathologist could not specify the subgroups of the disease. Survival curves were calculated by the Kaplan-Meier method. The statistical significance of each variable was tested by the log-rank test. The distribution of patients by prognostic variables and 3, 5 and 10 year survival rates are shown in Table V. Survival curves according to the most important characteristics of Table V are given in Figures 1-4. The relation between the histologic subtype and sex were statistically insignificant. The clinical group was found to be the factor most strongly related to survival ($p<0.001$). The estimated survival rates at five years were 66, 49, 37, and 12 percent in Clinical Groups I to IV, respectively (Fig. 1). The second most important factor was age ($p<0.001$). The outcome of infants less than one year of age was worse than

Table I: Age and Sex Distribution of Patients with RMS

Sex (M/F)	158/97 (1.6/1)
Median age	5.4 yrs
Age range	15 days - 17 yrs
Age groups (yrs)	
< 1	14
1-5	131
6-10	71
≥ 11	39
Total	255

Table II: Primary Site at Presentation of Patients with RMS

Site	n	(%)
Head and neck	125	(49)
Nonparameningeal	50	
Parameningeal	37	
Nasopharynx	26	
Orbit	12	
Genitourinary tract	32	(13)
Bladder-prostate	19	
Vagina-uterus	6	
Paratesticular	7	
Extremities	37	(15)
Trunk	20	(7)
Other	41	(16)
Total	255	(100)

Table III: Histologic Subtypes of Patients with RMS

Histology	n	%
Embryonal	137	(53.7)
Alveolar	42	(16.4)
Botryoid	18	(7)
Pleomorphic	14	(5.4)
Undifferentiated	44	(17.2)

Table IV: Clinical Group Distribution of Patients with RMS

Clinical Group	n	%
I	15	(6)
II	74	(29)
III	139	(54)
IV	27	(11)

Table V: Survival Rate of Patients with RMS

Characteristics of Patients	n	Survival (%) 3 years	5 years	10 years	p
Age (median 5 yrs)					<0.001
<1	14	18	0	0	
1-5	131	52	48	39	
6-10	71	49	40	40	
≥ 11	39	51	40	40	
Sex					>0.05
Male	158	45	41	39	
Female	97	48	44	41	
Primary site					=0.005
Orbit	12	66	66	66	
Head and neck	125	43	36	42	
Genitourinary system	32	68	68	68	
Extremity	37	58	48	40	
Trunk	20	48	32	32	
Retroperitonium	29	38	38	30	
Histology					>0.05
Botryoid	18	56	53	53	
Embryonal	137	49	42	37	
Pleomorphic	14	51	47	47	
Alveolar	42	43	34	28	
Clinical group					<0.001
I	15	83	66	66	
II	74	61	49	49	
III	139	40	37	37	
IV	27	25	12	0	
Treatment protocols					>0.05
Classic VAC	116	42	29	22	
pulse-VAC	88	62	60	57	
modified-AVAC	37	68	64	–	

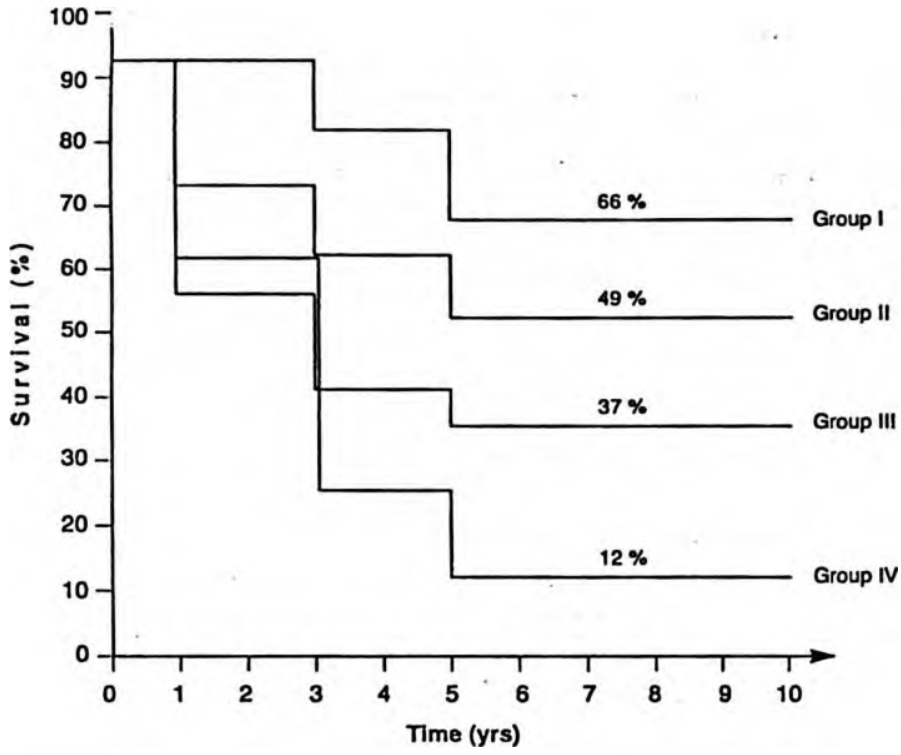

Fig. 1: Survival for RMS patients according to clinical group.

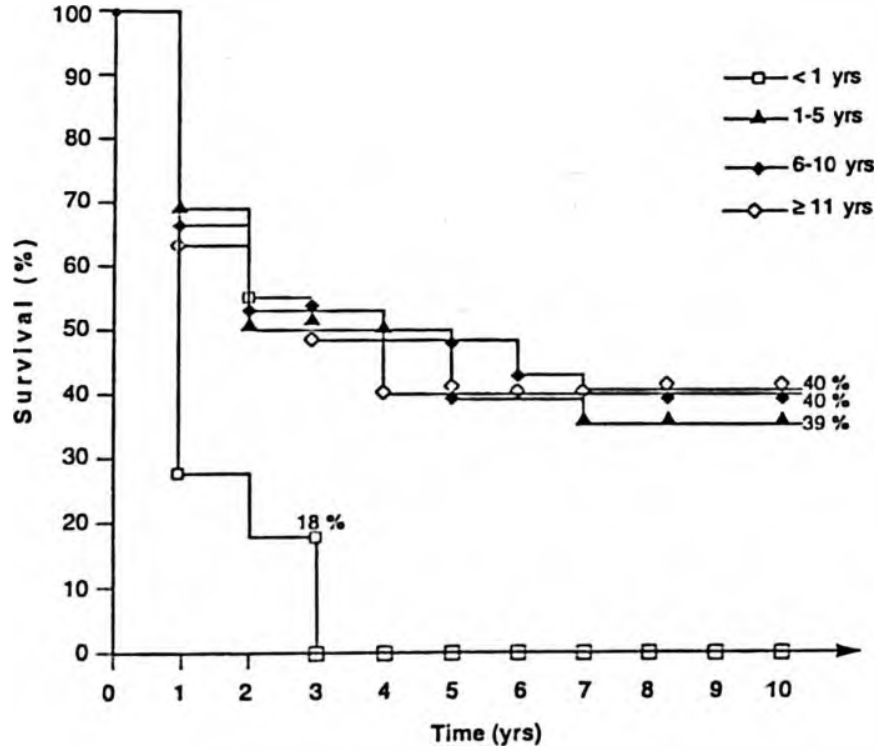

Fig. 2: Survival by age of patients with RMS.

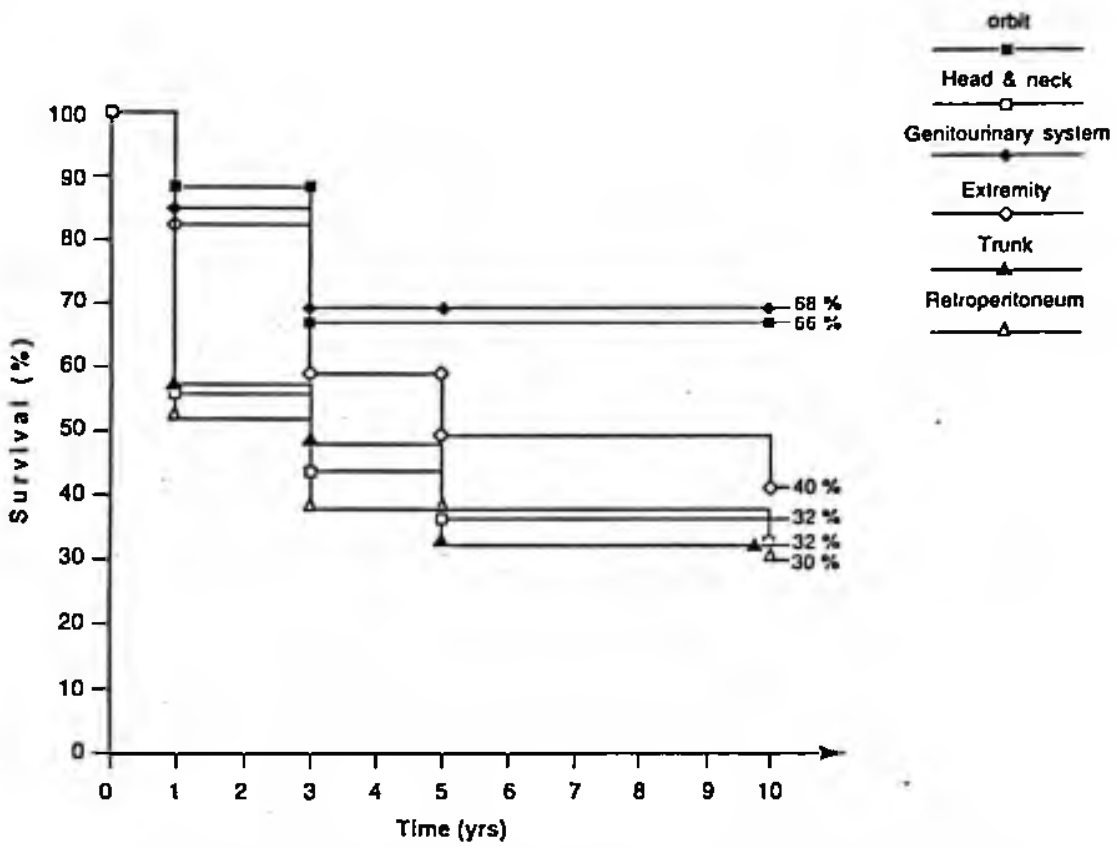

Fig. 3: Survival for RMS patients according to primary sites of tumor.

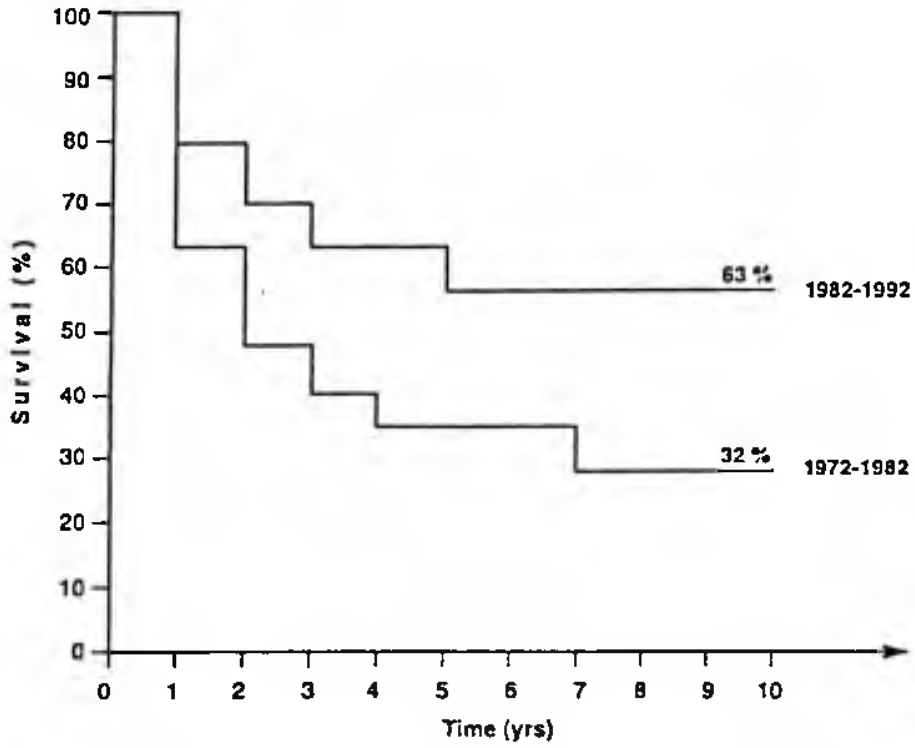

Fig. 4: Survival of children with RMS according to the years

that of older patients (Fig. 2). There was no significant relation between age and survival present except in this group. The overall survival was 27 percent in the first year. All patients in this group (n=14) died within three years after diagnosis. The third significant factor was the primary site. Figure 2 gives survival curves by primary site in all patients. The best survival was observed in patients with primary tumors of the orbit and genitourinary tract. The estimated rates of survival at five years, in decreasing order by primary site, were genitourinary tract 68 percent, orbit 66 percent, extremity 48 percent, head and neck (excluding orbit) 36 percent, and trunk 32 percent. Three different chemotherapeutic regimens were used depending on the year. There was no significant difference between the two regimens (pulse-VAC versus AVAC) in terms of survival. A significant difference with respect to survival was detected between those treated during the first ten years (1972-82) and the second ten years (1982-92), $p<0.005$ (Fig. 4).

Recurrences and/or metastatic spread: Tumor recurrence in children with localized disease at presentation occurred in the 58 patients (26%). The median time for tumor recurrence was 15.5 months. Metastases plus relapses developed in 54 patients (21%). The most common metastatic site was the lungs. The recurrence or metastases of disease occurred in 68 percent of patients within one year of diagnosis.

Ninety-six of 255 patients died during the follow-up period. Progressive disease and infection were the major causes of death (Table VI). Relapse sites and end results are shown in Table VII.

Although we did not intend to report treatment toxicities here, one patient who developed a second malignancy (osteosarcoma) at 12 years within the radiation field and died of this progressive disease deserves mentioning[8].

Discussion

In our series, the characteristics of the patients were similar to those of other series published in recent years in term of age range, sex ratio, and distribution of primary sites[6,9].

Table VI: Causes of Death in 96 Patients with RMS

Progressive disease	37
Infection	24
Postoperative (first 7 days)	4
Unknown	18
Other	13

Table VII: Relapse Patterns and Results in Patients with RMS

Local primary site	58
Pulmonary	32
Disseminated relapse (Local + Distant)	16
Other	6
Outcome of relapsed patients	
Exitus	17
Lost to follow-up	61
Alive	34

As would be expected, survival is inversely correlated with extent of disease in this retrospective analysis as well as in patients treated by combined modality therapy. The other significant prognostic factor was the primary site. The best survival was in patients having primary tumors of the orbit and genitourinary tract. In 1983 Kingston et al[10] concluded from a group of 73 patients that the major prognostic factor was the stage, but that histological type and primary site were not related to survival. The largest series is composed of 1,062 patients entered in the IRS-III and was reported in 1995 by Gehan et al[11]. The major prognostic factors were the clinical group and primary site, in contrast to histology which was not significant in this series.

It is interesting that age appeared to be an important prognostic factor in our series. The outcome of infants under one year of age was worse than that of older patients, due to life-threatening and fatal toxicities being more common in infants of that age. A similar result was reported by Ragab et al[12]. In their series, infants with rhabdomyosarcomas had a higher mortality rate than older children. Stow et al[13] and Koscielniak et al[14] had previously reported a slightly better prognosis in younger patients.

Sex and histologic type failed to be of prognostic importance in the present series; a similar result was reported in the IRS-III study[11]. Few studies have investigated the influence of histology on prognosis in childhood rhabdomyosarcoma. Patients with alveolar histology were reported to be associated with markedly decreased survival[15].

Thus, in our retrospective study, the analysis of survival of patients with RMS showed that age, stage and primary site were strongly related to prognosis. A meta-analysis was made by Rodary et al[16] on CWS-81 data, and data from the SIOP, IRS-II and Italian study (ICS). The univariate analysis showed that tumor

size, T (tumor) status, and primary site were related to prognosis in all the studies. In addition, the involvement of regional lymph nodes was found to be of prognostic importance when the data of all four studies were analyzed together. However, we could not investigate this in our series.

Improved survival rate in children with rhabdomyosarcoma has been obtained by using intensive-pulsed chemotherapy. The long-term survival rates in our series were about 42 percent with classic VAC, 62 percent pulse-VAC, and 68 percent modified AVAC protocol. Although modified AVAC regimen appears more effective than the others, the difference is not significant ($p>0.05$). German investigators[17] treated 225 patients with RMS from 1981 to 1986 using therapy similar to that in IRS-II (i.e., VAC plus adriamycin with central nervous system prophylaxis for parameningeal disease). Event-free survival rates by clinical group (I through IV) were 81, 68, 56 and 11 percent, respectively.

The overall results of this retrospective study display a significant improvement with respect to survival over time in our institution. We found survival at ten years was 32 percent before 1982 and 63 percent in the second ten years (after 1982). Despite this appreciable progress, we need more effective approaches in this tumor, especially in groups III and IV patients with rhabdomyosarcoma.

REFERENCES

1. Young JL Jr, Ries LG, Silverberg E, et al. Cancer incidence, survival, and mortality for children younger than 15 years. Cancer 1986; 58: 598-602.
2. Lanzkowsky P. Rhabdomyosarcoma and other soft tissue sarcomas. Manual of Pediatric Hematology and Oncology (2nd ed). New York: Churchill Livingstone Inc. 1995: 453-476.
3. Raney RB, Tefft M, Hays DM, Tricbe TJ. Rhabdomyosarcoma and the undifferentiated sarcoma. In: Pizzo PA, Poplac DG (eds). Principle and Practice of Pediatric Oncology (2nd ed). Philadelphia: Lippincot Com.; 1992: 769-794.
4. Mameghan H, Fisher R, Tobias V, et al. Local failure in childhood rhabdomyosarcoma and undifferentiated sarcoma: prognostic factors and implications for curative therapy. Med Pediatr Oncol 1993; 21: 88-95.
5. Lawrence W Jr, Gehan EA, Hays DM, Beltangady M, Maurer HM. Prognostic significance of staging factor of the UICC staging system in childhood rhabdomyosarcoma: a report from the Intergroup Rhabdomyosarcoma Study (IRS II). J Clin Oncol 1987; 5: 46-54.
6. Pelo R, Pike MC, Armitage P, et al. Design and analysis of randomized clinical trials requiring prolonged observation of each patient. Br J Cancer 1977; 35: 1-39.
7. Manter N. Evaluation of survival data and two new rank order situations arising in its consideration. Cancer Chemother Rep 1966; 50: 163-170.
8. Atahan L, Akyol FH, Gürkaynak M, et al. Post-irradiation osteosarcoma of the iliac bone: a case report. Turk J Pediatr 1989; 31: 227-231.
9. William MC, Lisa G, Mohan SB, et al. The Intergroup Rhabdomyosarcoma Committee. Prognosis in Children with Rhabdomyosarcoma: a report of the intergroup rhabdomyosarcoma studies I and II. J Clin Oncol 1990; 8: 443-452.

10. Kingston JE, McElvain TJ, Malpas JS. Childhood rhabdomyosarcoma: experience of the Children's Solid Tumour Group. Br J Cancer 1983; 48: 195-207.

11. Gehan WC, Ragab AH, Dicmen PS, et al. The Third Intergroup Rhabdomyosarcoma Study. J Clin Oncol 1995; 13: 610-630.

12. Ragab AH, Heyn R, Tefft M, Hays DN, Newton WA Jr, Beltangady M. Infants younger than 1 year of age with rhabdomyosarcoma. Cancer 1986; 58: 2606-2610.

13. Stow WW, Sullivan MP, Ried HC, et al. Prognosis in childhood rhabdomyosarcoma. Cancer 1970; 25: 1384-1390.

14. Koscielniak E, Harms D, Schmidt D, et al. Soft tissue sarcomas in infants younger than 1 year of age: a report of the German Soft Tissue Sarcoma Study Group (CWS-81). Med Pediatr Oncol 1989; 17: 105-110.

15. Newton WA, Jr, Soule EH, Hamoudi AB, et al. Histopathology of childhood sarcoma, Intergroup Rhabdomyosarcoma Studies I and II: clinicopathologic correlation. J Clin Oncol 1988; 6: 67-75.

16. Rodary C, Gehan EA, Flamant F, et al. Prognostic factors in 951 nonmetastatic rhabdomyosarcoma in children: a report from the International Rhabdomyosarcoma Workshop. Med Pediatr Oncol 1991; 19: 89-95.

17. Treuner J, Kühl J, Beck J, et al. New aspect in the treatment of childhood rhabdomyosarcoma: results of the German Cooperative Soft-Tissue Sarcoma study (CWS-81). Prog Pediatr Surg 1989; 22: 162-173.