Clinical Characteristics and the Prognosis of Childhood Rhabdomyosarcoma in 60 Patients treated at a Single Institute

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Abstract- Rhabdomyosarcoma (RMS) is the most frequent soft tissue sarcoma in children. The aim of study was to retrospectively review the treatment results of childhood rhabdomyosarcoma and identify prognostic factors. 60 children with rhabdomyosarcoma treated between 1996 and 2002 in Shafa Hospital were reviewed. The data were analyzed for clinico-epidemiological factors. Age, gender, race, histology type, primary site, tumor size and intergroup rhabdomyosarcoma study (IRS) group were evaluated. The primary site of involvement was orbit in 6 cases (10%) head and neck nonparameningial in 12 cases (20%), parameningial region in 12 cases (20%). The histological findings were as follows: 12 cases (72.5%) for embryonal, 6 cases (10%) for alveolar and 11 cases (17. 5%) for botryoid type. With respect to the IRS III (15%) were group II, 32 (52.5%) were group III and 24 cases (40%) were group IV. The 5-year survival rate was 47.9%. Primary tumor site (P=0.0003), and histology (P=0.05) were associated significantly with survival after recurrence. Among the variables, age, gender, regional lymph node involvement, and IRS group did not affect 5-year survival but the type and time of recurrence (P=0.0002), and its relation with therapy (P=0.0001) were associated with survival. This study showed that overall survival for rhabdomyosarcoma is dependent on histological subtype, primary site, disease group, duration of disease before treatment. The outcome for infant with RMS is less satisfactory than older children and the patients aged 1-9 years had the best 5 year survival.

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Introduction

Rhabdomyosarcoma (RMS) is the most common pediatric soft-tissue sarcoma, with an incidence of 4.6 per million in children 0-14 years old, and it constitutes 5. 8% of all malignant solid tumors in children (1-3). Among the extra cranial solid tumor, RMS is the third most common neoplasm after neuroblastoma and Wilms' tumor (4). It is highly invasive locally and has a high propensity for local recurrence. Almost two thirds of cases of RMS are diagnosed in children 6 years of age or younger with a smaller incidence peak in early mild adolescence. Although these tumors may rise virtually any where in the body, there are certain distinctive cluster of features regarding age at diagnosis, site of primary tumor, and histology. Collaborative studies of RMS have improved cure rate, especially for patients with locally extensive but unrespectable tumors. Survival has dramatically increased during the past 20 years; however, improvements in disease control are still needed for the majority of patients (approximately 65%) with gross residual disease after resection or metastatic disease at the time of diagnosis (1,4). An international study confirmed previous reports of radical and gender differences in the incidence of RMS (5) and we found that our patient are referred to us in advanced stages thus we conducted this study to evaluated the treatment results in our patients and identify prognostic factors that affect treatment outcome and overall survival in this ethnic group.

Patients and Methods

The records of 60 children with rhabdomyosarcoma treated between 1996 and 2002 in Shafa Hospital of Ahvaz city were reviewed. The data were analyzed for

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clinico-epidemiological factors. Age at diagnosis (<1 years, 1-9 years, and ≥10 years) and recurrence, race, gender, histological subtype, primary tumor site, tumor size and intergroup rhabdomyosarcoma study (IRS) group were evaluated. Patients were staged following surgery based on clinically and pathologically determined extent of disease and degree of initial surgical resection, according to criteria of IRS clinical staging system(6) (table 1). For the purpose of this study, recurrences were defined as early (<18 months after first diagnosis) or late (≥18 months after first diagnosis). Time to recurrence occurred further according to whether the recurrence before (on therapy) or after (off therapy) treatment was completed.

Treatment approaches to RMS incorporated surgery, radiation therapy, and chemotherapy. All the patients' received chemotherapy. It always started immediately after surgery or as upfront treatment in inoperable or metastatic patients. Patients with stage I, II orbital and stage I para-testicular area embryonal disease received 32 weeks of vincristine 1.5 mg/m^2 weekly, actinomycin-D 0.013 mg/kg day 1 to day 5 every 21 days without radiation therapy (7). Patients with other sites received 52 weeks of chemotherapy and radiation therapy on week 13 with 4140 cGy for stage I and II, and 5040 cGy for stage III and IV by convectional fractionation radiation therapy and treatment volumes included the tumor bed and a 2cm safety margin at least (8). Chemotherapy regimens included VAC (Vincristine 1. 5 mg/m^2 weekly, actinomycin-D 0.013 mg/kg/day day 1 to day 5 and cyclophosphamide 2. 2 mg/m^2 *i.v.* with mesna every 21 days), VAI (vincristin, actinomycin-D and ifosfamide 1. 8 mg/m^2 *i.v.* day 1 to day 5 with mesna) or VIE (vincristin, ifosfamide and etoposide 100 mg/m^2 *i.v.* day 1 to day 5) (9,10). Relapsing cases received palliative radiation therapy and second line chemotherapy (cisplatin 100 mg/m^2 *i.v.* divided over 2 days, etoposide 100 mg/m^2 *i.v.* day 1 to day 3 to be recycled every 21 days) for 6 cycles (11). The duration of chemotherapy depended upon the stage, histology, and primary site. It ranged from 24 to 48 weeks.

The patients were followed-up every 3 months for 5 years with median follow-up period of 36 months by chest X-ray, abdominopelvic sonar, CT scan, cerebrospinal fluid cytology for head and neck cases and liver and kidney profiles. Follow-up was updated at 2007. Overall survival (OS) after recurrence was estimated from the time of first disease recurrence to death or last follow-up evaluation. Death due to any cause was considered an event. Prognosis was defined according to the duration of OS. The overall survival was estimated by the method of Kaplan and Meier (12). The surviving patients were censored at the date of the last follow-up. The generalized Wilcoxon test was used to evaluate significance. A $P<0.05$ was considered statistically significant. Descriptive statistics were presented as number and percentage (frequency distribution).

Results

Regarding gender, 37 (61.66%) cases were male and 23 (37. 33%) cases were female. 28 cases (45%) were Fars and 31 cases (55%) were Arab. Their ages on admission ranged from 5 months old to 14 years old (mean: 5.1 ± 3.4 years). The primary site was the orbit in 6 (10%) cases, the nonparamenangeal head and neck in12 (20%) cases, the paramenigeal region in 13 (20%) cases, the extremities in 5 (8%) cases, the genitourinary region in 7 (11. 5%) cases, and 22 (35%) other cases.

Table 1. IRS- post surgical grouping classification

Group 1	**Localized disease, completely resected, no microscopic residual:**
	A- Confined to site of origin
	B- Infiltration beyond site of origin
Group II	Total gross resection:
	A- Grossly resected tumors with microscopic residual tumor
	B- Regional disease , completely resected, with nodes involved, and/or tumor extension into an adjacent organ
	C- Regional disease with involved nodes, grossly resected, but with evidence of microscopic residual tumor
Group III	Incomplete resection or biopsy with gross residual
Group IV	Distant metastases present at onset

The histological findings were as follow: 43 (71. 5%) embryonal, 6 (10%) alveolar, 11(17.5%) botryoid type. With respect to the clinical group, 4 (15%) cases were group II, 32 (52.5%) cases were group III, and 24 (40%) cases were group IV. Large tumor size (>5 cm) presented in 58.33% of cases. 31 (51.5%) cases have involvement of lymph nodes. Bone marrow involvement was seen in 9 (15%) cases. All cases received adjuvant chemotherapy.

Table 2. Five-year survival rated by prognostic variable in 60 Rhabdomyosarcomas

Variable	No. of patients	5-Yr OS (%)	*P* value
Age			NS
<1 yr	4	13. 9	
1-9 yrs	48	40. 1	
>10 yrs	8	27. 3	
Gender			NS
Male	37	37. 8	
Female	23	35. 4	
Histology			0. 05
Embryonal	43	70. 8	
Alveolar	6	12	
Botryoid	11	73. 1	
Primary site			0. 0003
Orbit	6	57. 2	
Head & neck	12	51. 3	
Parameningeal	13	41. 2	
Extremities	5	25	
Genitourinary	7	79. 8	
Others	22	28. 9	
IRS group			0. 049
II	4	71	
III	32	60	
IV	24	22. 1	
Tumor size			0. 0007
≤5 cm	25	43. 1	
>5 cm	35	24. 2	
Time from diagnosis to recurrence			0. 0002
Early(<18 month)	31	20. 3	
Late(≥ 18 months)	29	43. 2	
Recurrence & treatment			0. 0001
Recurrence on therapy	13	10. 9	
Recurrence off therapy	47	37. 4	

OS: overall survival

The 5-year survival rate for all patients was 49. 8%. The5-year survival rate for prognostic variable is given in Table II. An assessment of prognosis according to age showed that the 5-year survival rates were 13.9% for less than 1 year of age, 40.1% for 1-9 years of age, and 27.3% for more than 10 years of age. There were no differences between the groups. As for the prognosis according to the histological findings, the 5-year survival rates were 70.8% for the embryonal type, 12% for the alveolar, and 73.1% for the botryoid type. The prognosis according to the primary site, the 5- year survival rates were 57.2% for the orbit, 51.3% for the head and neck, 41.2% for the paramenigeal region, 25% for the extremities,79.8 % for the genitourinary region, and 28.9% for the others. Out come was the best among patients with primary tumors nonparameningeal of the orbit, genitourinary, intermediate among patients with tumors arising in other head and neck sites and the worst among patients with extremity, parameningeal and other($P<0.05$). Regarding to prognosis according to clinical group, the 5- year survival rates were. 71. 4% for grade II, 60.2% for grade III, 22.3 % for grade IV). Primary tumor site ($P=0.0003$), and histology ($P=0.05$) and IRS group ($P=0.049$) were associated significantly with survival after recurrence. Among the variables, age, gender, regional lymph node involvement, and did not affect 5-year survival but the type and time of recurrence ($P=0.0002$), and its relation with therapy ($P=0.0001$) were associated strongly with survival.

Discussion

Rhabdomyosarcoma is the most common soft tissue tumor in childhood. However, the relative rarity of this tumor, as well it's marked clinical and biologic heterogeneity (*i.e.* numerous primary sites, varied extent of disease at presentation) makes it difficult to treat such tumors (4).

In our current study: male constituted 61. 66% of cases (37 cases) and females constituted 38.33% of the cases (23 cases). The male to female ration was 1.6:1. These results are close to the work of Ruymann and Groves where male constituted 71.4% and females 28. 6% of cases (13) and to the study of ABD EL-AAL where male constituted 63.6% and females 36.4% of cases (14). In Shouman *et al.* study, the male to female ratio was 1.5:1 (15). In the IRS-IV, the male to female ration was 1.6:1 (16).

In the present study the most frequent site was the head and neck region, which accounted for 30% (Orbit 10%, non-orbit non-parameningeal 20%), and

parameningeal (20%). This was comparable to an ABD EL-AAL study where head and neck 36.4%, abdomen and genitourinary tract 23.6% and extremities 16.3% (14). In the study of Shoumaan *et al*. the most frequent site was the head and neck region, which accounted for 42% (Orbit 17%, non orbit non-parameningeal 16%), and parameningeal (9%) (15). In the IRS-III, the orbit constituted 10%, non orbit non-parameningeal 10% and parameningeal 15% (17). In the study of Suita *et al.* 56.3% for the head and neck, 43.8% for the parameningeal region, 12.5% for the extremity, 58.3% for the genitourinary and 30.5 R for the others (18). This contradicts the work of Akyuz *et al.* where the pelvi-abdominal area was the most common site of involvement (29%), followed by the extremities (15%) and than the trunk and the lung (5%) (19). Moreover, Nakada found that the most common site of involvement was pelvis (27.3% of cases), then the abdomen (23.8%) and then the head and neck (21.4% of cases) (20). This observation could be explained by differences in sample size between the two studies.

Embryonal RMS was the most frequent histological subtype in our study (71.5%). Similarly, it represented 62% in the study reported by Shoumann *et al.* (15) and in the Abd El-Aal *et al.* study of, embryonal histology constituted about 87.3% of the cases and Alveolar 12.7% of the cases (14). Unsimilar to the work of Callender *et al.* where embryonal histology constituted about 43. 2% of cases, alveolar 40.5% of the cases, mixed histology 2.7%, and unclassified histology in 13.5% of cases (21). Suita *et al*. reported 35. 8% for embryonal type, and 36. 8% for the alveolar type (18).

Tumor size >5cm was more frequent in our study (58. 33%) and this was similar to that of other studies in which 51% of tumors were >5cm (15,16). This reflected that most of our patients presented with advanced disease.

On multivariate analysis found that two characteristics of initial tumor (primary site, histology, and IRS-groups) and two characteristics of the recurrence (type and temporal relation with therapy) were independent prognostic factors affecting overall survival. Patients with a non-alveolar histology, primary tumor site different from parameningeal and other sites local recurrence, and recurrence off therapy had a better prognosis. These factors were in agreement with other published reports (14-16, 18, 22, 23).

Five-year overall survival (OS) was 49.8% %, in our study. The percentage of patients' alive 5-year after the ignition of therapy increased from 65% in IRS-III (17), and improved to 76% in IRS-IV (16). This can be explained by improvement of early diagnosis, staging work up and better chemotherapy regimens. In other study, the five- year OS was 74% (14), and in the study of Shouman *et al.* was 50% (15), in comparison to the work of Crist et al, where the 5-year OS was 77% (16). Also, with the work of Flamant *et al.* who attained a 5-year OS of 68% (24) and with the work of Suita *et al.* the 5-year survival rate was 39. 1% (18) and the study of Ferrari *et al.* were 61. 7% (25) and Badford *et al*. reported 73% (19) but in the study of Mazolini *et al.* reported 28.3% ± 8.7% (23).

The five-year OS for patient with ages more than 10 year was 27. 3%. These result were similar to the work of La Quaglia *et al.* and the work of Arndt *et al.* where the age of patient whether less than 10 years or more than 10 years had and impact on the five-year survival (27,28). All the studies agreed that patient's age 1-9 year had the best 5-year survival. This work also resembles with the works who stated that long-term survival was noticed with patients younger than 10 years of age (8,18,29).

The IRS introduced a clinical grouping system bases on the amount and extent of the residual tumor after initial procedure (1). When assessing the prognostic according to clinical group, patients with group I or II tumors fared better than those with group III or IV tumors. The 5-year survival rates were 71.4% for group II, 60.2 % for group III, and 22.3% for group IV. Our results differed to some degree, because the IRS clinical group dose not emerge as a risk factor even in univariate analysis, because our sample was less numerous and included fewer alveolar RMS. In comparison IRS-III reported the 5-year survival rates to be 93% for group I, 81% for group II, 73% for group III, and 30% for group IV, respectively (18). This can be explained by improvement of early diagnosis, staging work-up and better chemotherapy regimens. The second SIOP study, performed from 1984 to 1988, reported a 5-year survival rate of 89% for stage I, 63% for stage II, and 42% for stage III (24). In the study of ABD EL-AAL *et al*. 50 year OS for group I, II, and III was 86%, 77% and 65% respectively (14); this coincides with the work of Neville where group I, II, and III was 70%, 65% and 55% respectively (30). In addition the work coincides with the other studies; who reported the best survival results for patients with stage I and II (15,19).

Histological variant is a strong prognostic factor. Patients with favorable histological subtypes as Botryoid and embryonal showed 5-year OS of 73.1% and 70.8%, while unfavorable histological variants as Alveolar showed 12%, respectively. Patients with Embryonal Rhabdomyosarcoma have not always enjoyed excellent survival in IRS studies. In other study the 5-year OS for

Embryonal histology was 80. 6% and 65% for Alveolar histology (14); these result correlate with the work of Pappo *et al.* , where the 5-year survival for Embryonal was 64% and Alveolar histology, it was 26% (31). Mazzolini *et al.* should be noted that children with botryoid tumors had an encouraging 64% five-year survival rate (22). Shouman *et al*. confirmed that patients with recurrent Embryonal tumors fared significantly better (15). Sutia *et al.* reported 5-year survival for embryonal was 35.8% and Alveolar histology, it was 36. 8% (18).

Initial tumor site is an important variable after recurrence. In our study the 5-year OS 51.3% for the head and neck, 41.2% for the parameningeal, 25% for the extremity, 79.8% for the genitourinary region and 28.9% for the others. Outcome was the best among patients with primary tumors of the orbit, genitourinary, intermediate among patients with tumors arising in other head and neck sites and the worst among patients with extremity, parameningeal and other. In the other study patients with genitourinary RMS and orbit RMS had the best outcomes (60% and 56% respectively), whereas patients with other and Paramenigeal sites had the worst outcomes (18. 8% and 0% respectively) (22). The 5-year OS 56. 3% for the head and neck, 43.8% for the parameningeal, 12.5% for the extremity, 58.3% for the genitourinary region, and 30.5% for the others (18). In the work of Shouman *et al.* patients with GU-non BP had the best 5-year FFS (85%) while extremities, trunk and retropritoneal sites had the worst results which are attributed to advanced disease at presentation and predominance of unfavorable histology as alveolar subtype which constituted more than half the tumors in these sites(15). In the IRS-III, 5-year FFS was 84% for genitourinary sites and 47% for the extremities 43% in SIOP (24) and 66% in IRS-III (17).

In the current study, the timing of the recurrence also was important, as also noted in study by Mazzoleni *et al.* who reported that children who developed recurrent disease after completing chemotherapy had a significantly higher survival rate compared with patients who had developed recurrences while they were receiving chemotherapy (19% vs. 2. 7%; $P<0.05$) (22). Recurrence during treatment indicates a biologically more aggressive tumor or selection of chemo resistant clones that make retrieval therapy very difficult. In conclusion, our treatment results were inferior compared to IRS-studies as the patients were treated on individual bases and standardized protocol. Treatment according to the results of IRS-IV would achieve better results. Despite the advances in the therapy of Rhabdomyosarcoma some cases with Rhabdomyosarcoma experience progressive or relapsing disease, which eventually have a fatal end.

The factors determining the 5-year survival after relapse at the time of initial diagnosis include histological subtype, primary site, disease group, duration of disease before treatment. The outcome for infant with RMS is less satisfactory than older children.

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