# Survival rate of children with rhabdomyosarcoma and prognostic factors

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***Background:*** **Rhabdomyosarcoma is the most frequent tumor of soft tissue in children. The survival rate of the patients is significantly increased since the 1970s. This study was undertaken to evaluate the 5- and 10-year survival rates of patients with rhabdomyosarcoma in a single center in Iran.**

***Methods:*** **A total of 77 children with rhabdomyosarcoma up to 15 years old who had been treated at the Hematology and Oncology Department in Ali Asghar Children Hospital from 1993 to 2003 were evaluated for their age and gender, as well as histology, stage and primary site of the tumor at diagnosis.**

***Results:*** **The mean age of the patients was 6.58 years (SD=4.02, median 6 years). In this series, 46 patients (59.7%) were male and 31 (40.3%) female, and the mean survival time of patients was 8 years (95% CI: 8-9). The 5-year survival rate was the highest in patients with localized tumor, stage I and II (82.25% and 86.88% respectively). The survival rate of patients with embryonal tumor was 86.8%, in those with primary orbital tumor was 94%, and in those with genitourinary tumor was 85.71%. The 5- and 10-year overall survival rates were 79.54% and 77.92%, respectively.**

***Conclusions:*** **Children with rhabdomyosarcoma of lower stage, embryonal histology, and orbital and genitourinary primary sites had a better survival rate. Poor prognosis was associated with metastasis of the tumor at the time of presentation, alveolar histology (48%), and tumor of the extremities (58%). In our study, only the stage of the tumor was significantly different in the variables (*P*=0.0077) because of the small number of patients. Children who survived the first 5 years after diagnosis were found to have an excellent survival rate.**

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***Key words:*** **rhabdomyosarcoma;**
**survival rate;**
**age;**
**primary site;**
**stage;**
**pathology**

## Introduction

Rhabdomyosarcoma (RMS) is a heterogeneous malignant tumor. RMS cells arise from undifferentiated mesodermal tissue and primarily in striated muscle but can originate in the tissue that does not normally contain striated muscle. The annual incidence of rhabdomyosarcoma is four to seven per million children of 20 years old or younger. Approximately 350 new cases are diagnosed in the USA each year.[1] RMS is the third most common extracranial solid tumor in children following neuroblastoma and Wilm's tumor.[2,3]

About two thirds of RMS cases are diagnosed in children aged 6 years or younger, with a smaller incidence peak in early mid-adolescence.[3] The tumor is slightly more common in males than in females.[3] Nearly 53% of patients have embryonal and 20%-30% have alveolar subtypes of the tumor.[3,4] Embryonal subtypes are often localized with a favorable prognosis; in contrast, more often alveolar subtypes present with distant metastasis and less favorable prognosis.[1]

Prior to the introduction of anti-neoplastic drugs, surgery played a principal role in the treatment of patients with RMS. In 1972, an intergroup rhabdomyosarcoma study (IRS) began an ongoing series of collaborative clinical treatment regimens that improved the outcomes of children with early stage tumor.[5] The discovery of effective chemotherapy made the treatment of disseminated tumors possible and improved the overall survival from 25% in 1970 to 70% in 1991.[6] The present management of

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children with RMS includes surgery, radiation, and chemotherapy. Each of these modalities has played an important role in improving survival rate and each has evolved or changed over the past several decades.[7] The purpose of this study was to evaluate the 5- and 10-year overall survival rates in children treated at our department and also the related factors.

## Methods

### Data source, study population and data analysis

From 1993 to 2003, 77 patients with RMS were diagnosed and treated at Hematology Oncology Department of Ali Asghar Children Hospital. Their age at diagnosis, gender, primary tumor site, histological subtype, stage at diagnosis and treatment were analyzed. The age at diagnosis was assessed as a categorical variable at 4 levels: <1 year; 1-4 years; 5-9 years; and 10-15 years. Primary sites of RMS were grouped: head and neck with orbit and parameningeal sites, genitourinary tract (GUT), retroperitoneum, trunk and extremities. Histologically, the tumors were classified as embryonal (including botryoid sarcoma), alveolar and others. Pre-treatment and post-treatment for staging consisted of complete history, physical examination, complete blood count, urinalysis, serum electrolytes and biochemistries, MRI and CT of primary lesions, chest CT, skeletal survey, bone scan, and bilateral bone marrow aspiration and biopsy.

The patients were treated according to the IRS protocol (most patients treated with IRS-IV): primary surgery or debulking biopsy followed by chemotherapy and radiotherapy (between 9-12 weeks of chemotherapy except in patients with parameningeal tumors and intracranial extension that was given radiotherapy at day 0). In patients without primary tumor of head and neck as well as orbit and parameninge, only 9 patients received primary chemotherapy and radiotherapy after biopsy because of their advanced stage.

The duration of therapy from 1993 to 2003 has changed: in the first year of study, the duration was 1 year for stage I and II, and 2 years for stage III and IV; but afterwards 12 months for all stages. Chemotherapy was prescribed according to the stage of disease. The following agents were used: vincristin, actinomycin D (VA), vincristin+actinomycin D and cyclophosphamaide (VAC), VAC+doxorubicin (ADR), and ifosfamaide (IF)+etoposide (VP16).

The survival time (i.e., follow-up time) was measured by years from the date of diagnosis to either the date of death from any cause or a censoring date, or to December 13, 2003 when the patients were alive. The duration of follow-up from the initial diagnosis to the end of the study was 10 years. The survival rate of patients was calculated using the Kaplan-Meier method.[8] Cox regression was used to evaluate the factors that affect survival rate. SPSS 11.5 software was used for analysis, and a $P$ value <0.05 was considered statistically significant.

## Results

In the 77 patients with RMS up to 15 years old, their mean age at diagnosis was 6.58 years (SD=4.02) (Table 1). Forty-six patients (59.7%) were male and 31 (40.3%) female. Eight patients (10.4%) were below one year, 18 (23.4%) 1-4 years, 32 (41.5%) 5-9 years, 18 (23.4%) 10-15 years, and 1 (1.3%) unknown.

**Table 1.** Characteristics of 77 patients up to 15 years diagnosed with RMS, 1993-2003

| Characteristics | Number of patients | % |
|---|---|---|
| Gender | | |
| Male | 46 | 59.7 |
| Female | 31 | 40.3 |
| Age at diagnosis | | |
| <1 | 8 | 10.4 |
| 1-4 | 18 | 23.4 |
| 5-9 | 32 | 41.5 |
| 10-15 | 18 | 23.4 |
| unknown | 1 | 1.3 |
| Histology | | |
| Embryonal | 59 | 76.6 |
| Alveolar | 15 | 19.5 |
| Others | 2 | 2.6 |
| unknown | 1 | 1.3 |
| Primary tumor site | | |
| Orbit | 18 | 23.4 |
| Parameninge | 11 | 14.3 |
| Head/neck | 17 | 22.1 |
| Genitourinary tract | 10 | 13.0 |
| Extremity | 11 | 14.3 |
| Retroperitoneum | 10 | 13.0 |
| Stage | | |
| I | 34 | 44.2 |
| II | 24 | 31.2 |
| III | 14 | 18.2 |
| IV | 5 | 6.4 |

**Table 2.** Primary sites in the genitourinary tract

| Primary sites | Number of patients |
|---|---|
| Bladder only | 4 |
| Bladder, uterus, ovary | 1 |
| Bladder and prostate | 2 |
| Right testicular tumor | 1 |
| Left paratesticular | 1 |
| Labia major | 1 |

The primary tumor site was as follows: head and neck in 46 patients (59.7%), retroperitoneum in 10 (13.0%), GUT in 10 (13.0%), extremities in 11 (14.3%). Of the 46 primary sites in head and neck, 18 (23.4%) in orbit, 11 (14.3%) in parameningeal non orbit, and 17 (22.1%) in other sites of head or neck. Of the 10 primary sites in GUT, only bladder in 4; bladder, uterus and ovary in 1; bladder and prostate in 2; right testicle in 1; left paratesticular in 1; and labia major in 1 (Table 2).

Immunohistochemically, histological subtypes of RMS were embryonal in 59 patients (76.6%), alveolar in 15 (19.5%), and small round cell in 2 (2.6%). In most patients, the tumors were in stage I and II. Stage I tumor was seen in 34 patients (44.2%), stage II in 24 (31.2%), stage III in 14 (18.2%), and stage IV in 5 (6.4%) (Table 1).

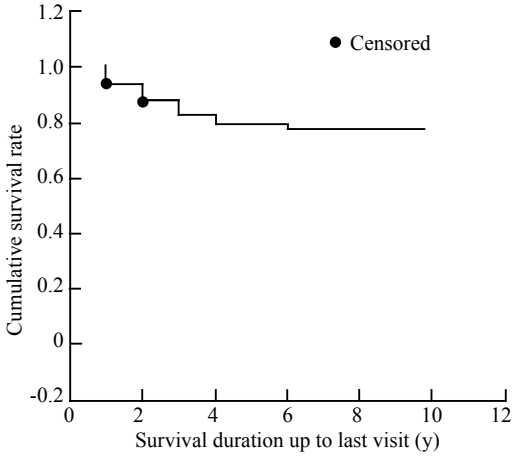


**Fig.** The cumulative survival rate of patients with rhabdomyosarcoma.

Treatment included surgery, radiotherapy and chemotherapy according to the primary site and stage of the tumor. VA was used in 6% of the patients, VAC in 20%, VAC+ADR in 55%, and IF+VP16+VCR in 19%. After the treatment, 18 patients (23.4%) relapsed, with a mean relapse time of 14.78±0.8 months. The shortest and longest time of relapse was 3 months and 24 months respectively. There was a significant relationship between the primary site and relapse ($P$<0.01).

The duration from initial diagnosis to the end of study was 10 years. The mean survival time of patients in this study was 8 years (95% CI). The 5- and 10-year overall survival rates for the 77 patients were 79.54% and 77.92% respectively (Fig.). For males, the 5- and 10-year survival rates were 75% and 72% respectively, with a mean survival of 8 years (95% CI: 7-9 years). For females, the 5- and 10-year survival rate was 85%, with a mean survival of 9 years (95% CI: 8-10 years). No significant difference was observed between males and females ($P$=0.33). The 5- and 10-year survival rates in patients below 1 year were 100%, 1-4 years 85%± 9%, 5-9 years 88%±6% and 10-15 years 100%. Other important factors are shown in Table 3.

## Discussion

In the 77 patients up to 15 years old, the mean age at diagnosis was 6 years. Most patients were male (59.7%) as reported by Punyko et al,[9] in contrast to the description of slightly more common in males than in females.[3] The 5-10 year overall survival rate was

**Table 3.** The 5- and 10-year survival rates of patients with rhabdomyosarcoma

| Factors | 5-year survival rate (%) | 10-year survival rate (%) | Mean (y) | 95% CI (%) | *P* value |
|---|---|---|---|---|---|
| Overall | 79.5 | 77.9 | 8 | 8-9 | - |
| Pathology | | | | | 0.12 |
| Embryonal | 86.8 | 86.8 | 9 | 8-10 | |
| Alveolar | 48.0 | 48.0 | 6 | 4-8 | |
| Round cell | 100.0 | 100.0 | 10 | - | |
| Stage | | | | | 0.007 |
| I | 85.8 | 82.2 | 9 | 8-10 | |
| II | 86.9 | 86.9 | 9 | 7-10 | |
| III | 64.8 | 64.8 | 7 | 5-10 | |
| IV | 20.0 | 20.0 | 4 | 1-7 | |
| First location of tumor | | | | | 0.15 |
| Orbital | 94.0 | 94.0 | 10 | 9-10 | |
| Parameningeal involvement | 57.1 | 57.1 | 7 | 3-10 | |
| Other sites in head & neck | 73.1 | 73.1 | 8 | 6-9 | |
| Retroperitoneum & trunk | 75.0 | 75.0 | 8 | 6-10 | |
| GUT | 100.0 | 85.7 | 9 | 8-10 | |
| Extremity | 58.4 | 58.4 | 7 | 4-9 | |
| Recurrence | | | | | <0.001 |
| Positive | 31.9 | 23.9 | 5 | 3-7 | |
| Negative | 92.2 | 92.2 | 9 | 9-10 | |

higher in females than in males, but the difference was not significant ($P$=0.32). Most of our patients at diagnosis were in stage I (44%), but stage III (48%) is more common than stage I as reported elsewhere.[3] We found that stage of the tumor, histological subtype, and the primary site are important predictors for survival of patients with RMS. Good prognosis is associated with localized disease, embryonal RMS, orbit and genitourinary primary tumor sites, whereas poor prognosis is associated with distant or metastatic disease, alveolar histology, and site of the extremities, retroperitoneum, trunk and parameninges. In Punyko's study,[9] patients aged 1-9 years at diagnosis showed good prognosis, those below 1 year and 10-19 years showed poor prognosis, as reported in two other studies.[6,10] In our patients, the result was different, the reason may be the low stage of the tumor at diagnosis and embryonal histology, moreover the small number of patients may have affected the result.

The most favorable site of tumors in our patients was orbit (94% survival). These tumors are known to have an excellent prognosis,[11,12] and only one of the patients with orbital involvement relapsed, and died from bone and liver involvement. Like other studies,[13,14] non-parameningeal head and neck tumors had a better prognosis of 73% and 57% respectively in our patients than the parameningeal ones. In the parameninges, the survival rate before the formation of the intergroup rhabdomyosarcoma study group was less than 25%, whereas the recent 5-year overall survival rate on the IRS was 73%,[15] and Arnold Paulino and his colleagues stated the 2- and 5-year survival rates were 78.9% and 45.7%.[16] In GUT, the 5-year survival rate in our patients was 85%, the trunk and retroperitonum 75%, and the extremities 58.5%. In Punkyo's study,[9] the 5-year survival rate for orbit was 86%, GUT 80%, retroperitoneum 52%, and extremities 50%.

In patients with embryonal RMS, the 5-10 year survival rate was 86.8%, and those with alveolar RMS 48%; those with alveolar RMS subtypes had a poor prognosis (53%).[17] In Punkyo's study, the 10-year survival rate of subtypes was 42%. Long-term prognosis for children with progressive or recurrent tumor is poor. The 3-year survival rate following a relapse was 15% in patients who had been diagnosed as clinical group II-IV.[9] Like other studies, the best result of this study was observed in localized tumors, stage I (82.2%) and stage II (86.88%), and 25.4% of the patients had a recurrence. All except two cases relapsed at primary site. Mazzoleni and colleagues[18] reported a local recurrence rate of 72%, and the mean time from diagnosis to recurrence was 17.8 months. The 5-year survival rate was 28.3%± 8.7%,[18] in contrast to 31.91% in our study.

In conclusion, by chemotherapy, radiotherapy and surgery, the outcome of RMS has been improved. Patients with embryonal histology, in stages I and II, primary sites at orbit and GUT may have a better prognosis. Tumor stage at diagnosis may be statistically different ($P$=0.0077). Despite the poor prognosis of certain subgroups, the overall 5-10 year survival rate for patients with RMS is relatively high.

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