Retinoblastoma Survival in Iran:  
10 Years Experience of a Referral Center

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Abstract

**Purpose:** To describe the survival characteristics and prognostic factors of patients with retinoblastoma in a referral center in Iran

**Methods:** From medical records, we retrospectively analyzed the data of 139 consecutive children diagnosed in our hospital between 1991 and 2001 as having retinoblastoma. Information on gender, laterality, age at diagnosis, presenting signs, tumor staging, treatment modality, survival rate, and family history were collected.

**Results:** Eighty-eight (63.3%) of the cases were unilateral and 51 (36.7%) of the cases were bilateral. The mean age overall at the time of diagnosis was 26.9 months; in unilateral cases, 32.7 months; and in bilateral cases, 22.8 months. The most common presenting signs were leukocoria (72.7%), strabismus (12.2%), and proptosis (7.9%). Fifty-one percent of patients had extraocular extension. The 5-year cumulative survival rate was 69.62% and the 10-year overall survival rate was the same as the 5-year survival rate. Patients with an age at the time of diagnosis of ≤2 years, with stage I and with positive family history had significantly better survivals both at the 5 and 10 years analysis (P<0.002, P<0.002, P<0.041 respectively). None of the patients developed a secondary neoplasm.

**Conclusion:** In this study the mortality rate of patients with retinoblastoma is higher than the reports from developed countries. Availability and quality of registration data on retinoblastoma need to be improved for effective quantitative evaluation of incidence and survival.

**Keywords:** Childhood, Retinoblastoma, Survival Rate, Risk Factor, Cancer

Introduction
Since the first reports on treatment of children with retinoblastoma, survival of these patients has improved dramatically.\textsuperscript{1,2} This lethal cancer in early 20\textsuperscript{th} century, was the pediatric cancer with the highest survival rate in 2003.\textsuperscript{3} Five-year survival rates of more than 90\% have been reported from the countries of the developed world.\textsuperscript{2-4} However, only about 5\% of the world’s estimated 20,000 retinoblastoma cases live in these countries.\textsuperscript{5} There are a few reports regarding the survival rate of retinoblastoma patients in underdeveloped and developing countries.\textsuperscript{6-12} Although the data from the 95\% of the worldwide retinoblastoma patients are relatively scarce, these reports emphasize on wide range of mortality rates between different regions of the world.\textsuperscript{8,12}

This study is a situation analysis of treatment and prognosis of patients with retinoblastoma in a single center in Iran, over a 10 years period before institutionalization of ocular oncology service in our hospital.

Methods
The medical records of 188 consecutive patients with retinoblastoma diagnosed and treated at the pediatric clinic of the department of ophthalmology, Iran University of Medical Sciences, Tehran, Iran, between August 1991 and August 2001 were reviewed. The study approved by the Institutional Review Board of our hospital.

All patients had to have baseline and frequent ocular examinations under anesthesia during follow-up period. To become eligible, all enucleated eyes had to undergo a full examination by an experienced pathologist. In patients in whom both eyes were preserved, diagnoses were based upon ophthalmological findings. At baseline, computed tomography scanning of the brain and orbit, lumbar puncture and bone marrow aspiration and biopsy and complete differential blood count were obtained for all bilateral patients. After availability of the magnetic resonance imaging (MRI), the scheduled workup included MRI of the brain. For unilateral patients only complete blood count was performed.

The data included gender, laterality, age at diagnosis, presenting signs, family history, degree of tumor differentiation (well differentiated, moderate differentiation and poorly differentiated), stage at diagnosis according to Grabowski-Abramson staging system,\textsuperscript{13} treatment modalities used, and survival rates.

Statistical analyses were performed using the SPSS software (SPSS for Windows 15; SPSS Inc, Chicago, IL, USA). Descriptive statistics for each variable was obtained. The Kaplan-Meier method was used to determine overall survival. Differences between groups were analyzed using Gehan-Wilcoxon test and were considered significant when two-sided P-value was less than 0.05.

Results
Altogether, there were 188 patients; however, 3 months follow-up at least was present for 139 patients with 190 involved eyes. The follow-up period ranged from 3 to 165 months (mean, 58.7±33.4 months). In total, 103 patients remained alive, and 36 patients died prior to the cut-off date (31 August 2001).

Sex, laterality, and family history
There were 82 boys (59\%) and 57 girls (41\%). A total of 88 cases (63.3\%) had unilateral involvement and 51 cases (36.7\%) had bilateral. In our study, 10 patients (7.2\%) had a positive family history of retinoblastoma; six of them had bilateral involvement.

Age at diagnosis
The mean age at diagnosis was 29.6±22.6 months (range 1 to 120 months, median=24 months). The mean patient age at diagnosis of the unilateral cases was 32.7±22.4 months, and that of the bilateral cases was 22.8±21.7 months.

More than 90\% of patients were diagnosed before the age of 5 years. For the unilateral cases, 92.5\% of patients were diagnosed before the age of 5 years. For the bilateral cases, 93.5\% of patients were diagnosed before the age of 4 years.

Presenting signs
The most common presenting signs were leukocoria (101 cases, 72.7\%), strabismus (17 cases, 12.2\%), proptosis (11 cases, 7.9\%), and red eye with tearing or pain (3 cases, 2.1\%). Six patients (4.3\%) were detected during routine eye examination.
Tumor staging
In 36 of the 139 cases, data on tumor staging were missing. Of the remaining 103 patients, 50 cases (48.5%) presented with intraocular diseases (stage I). 30 cases (29.3%) demonstrated stage II (orbital involvement). Twelve cases (11.6%) had intracranial metastasis (stage III) and 11 cases (10.7%) had hematogenous spread (stage IV). Detailed tumor staging and outcomes were summarized in table 1. The most common extraocular invasion sites were the orbit and central nervous system. No patient developed a secondary malignant neoplasm.

Mode of treatment
All patients received at least one mode of therapeutic modalities and no eye left to the natural course. Enucleation was performed in 101 cases (72.6%). Of these, 74 were unilateral patients. Four patients underwent bilateral enucleation. Six unilateral cases received radiation therapy after enucleation, when there was some evidence of tumor invasion beyond the section line. Three patients with bilateral tumors received external beam radiation therapy. Chemotherapy was used in 86 patients (61.8%). Eleven patients (7.9%) received local treatment using cryotherapy.

Survival analysis
The cumulative survival rate of 139 patients was 83.31% at 1 year, 77.33% at 2 years, and 69.62% at both 5 years and at 10 years (Figure 1). The survival rates of the patients with respect to different studied variables summarized in table 2.

Survival rates were significantly better in patients with an age at the time of diagnosis of ≤2 years (Figure 2), with stage I (Figure 3) and with positive family history both at the 5 and 10 years analysis.

<p>| Table 1. Spread of tumor and outcomes in 103 retinoblastoma cases (The stage is for the eye with more advanced stage in bilateral patients.) |</p>
<table>
<thead>
<tr>
<th>Stage</th>
<th>No. of patients</th>
<th>Deceased (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ia (retinal tumor, single or multiple)</td>
<td>26</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Ic (uveal extension)</td>
<td>24</td>
<td>2 (14.2)</td>
</tr>
<tr>
<td>IIa Orbital tumor</td>
<td>7</td>
<td>2 (28.5%)</td>
</tr>
<tr>
<td>IIb Optic nerve</td>
<td>23</td>
<td>7 (30.4%)</td>
</tr>
<tr>
<td>IIIa (positive cerebrospinal fluid alone)</td>
<td>1</td>
<td>1 (100%)</td>
</tr>
<tr>
<td>IIIb (mass lesion in central nervous system)</td>
<td>11</td>
<td>4 (36.3)</td>
</tr>
<tr>
<td>IVa (positive bone marrow alone)</td>
<td>10</td>
<td>3 (30%)</td>
</tr>
<tr>
<td>IVb (focal bone lesions with or without positive bone marrow)</td>
<td>1</td>
<td>1 (100%)</td>
</tr>
</tbody>
</table>

<p>| Table 2. Effect of different factors on overall survival in retinoblastoma patients |</p>
<table>
<thead>
<tr>
<th>Variable</th>
<th>5 years survival</th>
<th>10 years survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender: Male/Female</td>
<td>69.86% / 70.32% (P=0.5)</td>
<td>69.86% / 70.32% (P=0.5)</td>
</tr>
<tr>
<td>Laterality: Unilateral/Bilateral</td>
<td>83.02% / 62.67% (P=0.054)</td>
<td>83.02% / 62.67% (P=0.054)</td>
</tr>
<tr>
<td>Family history: Positive/Negative</td>
<td>100% / 66.95% (P=0.041)</td>
<td>100% / 66.95% (P=0.041)</td>
</tr>
<tr>
<td>Stage: I/IIC</td>
<td>92.25% / 69.08% (P=0.002)</td>
<td>92.25% / 69.08% (P=0.002)</td>
</tr>
<tr>
<td>Histological differentiation: well differentiated / moderate and undifferentiated</td>
<td>90% / 84.38% (P=0.1)</td>
<td>90% / 84.38% (P=0.1)</td>
</tr>
<tr>
<td>Presenting sign: leukocoria/ strabismus/ proptosis / routine exam</td>
<td>73.27% / 79.16% / 56.41% / 100% (P=0.5)</td>
<td>73.27% / 79.16% / 56.41% / 100% (P=0.5)</td>
</tr>
<tr>
<td>Age at the time of diagnosis: ≤2 years/ &gt;2 years</td>
<td>76.71% / 61.35% (P=0.002)</td>
<td>76.71% / 61.35% (P=0.002)</td>
</tr>
<tr>
<td>Surgery: positive/ negative</td>
<td>80.56% / 87.33% (P=0.3)</td>
<td>80.56% / 87.33% (P=0.3)</td>
</tr>
<tr>
<td>Chemotherapy: positive/ negative</td>
<td>79.08% / 90.12% (P=0.4)</td>
<td>79.08% / 90.12% (P=0.4)</td>
</tr>
<tr>
<td>Radiation: positive/ negative</td>
<td>75.63% / 83.10% (P=0.8)</td>
<td>75.63% / 83.10% (P=0.8)</td>
</tr>
</tbody>
</table>
Figure 1. Overall 5-year and 10-year survival rates of retinoblastoma patients were both 69.62%.

Figure 2. Five-year overall survival rate of patients with an age at the time of diagnosis of ≤2 years (76.71%) (Solid line) and age of more than 2 years at the time of diagnosis (61.35%) (Dashed line). In both groups, the 10-year overall survival rate was the same as the 5-year survival rate.
Figure 3. Five and 10-year survival rate of patients with stage I (92.25%) (Solid line) and stage ≥II (69.08%) (Dashed line). In both groups, the 10-year overall survival rate was the same as the 5-year survival rate, and the difference between groups was the same.

Discussion

Retinoblastoma is an eminently curable cancer and treatment is usually highly successful. Five-year survival rates for retinoblastoma have been in excess of 90% in the United kingdom, United States of America, and probably in other developed countries for some decades. However, the survival rate of retinoblastoma is still associated with wide variations in different countries in the world. The 3-year cumulative survival rate was reported to be 89.69% in Turkey. In a series of 68 cases in Singapore from 1968 to 1995, the 3-year survival rate was reported as 83%. Chang et al reported a 5-year overall survival rate of 80.9% in Taiwan. In some areas, however, the mortality rate is high. For example, the mortality rate in Malaysia is 55% in unilateral cases, and no patients with bilateral disease survive beyond 5 years. Our data showed that the 5-year survival rate in Iran was 69.62% and remained stable up to 10 years.

Similar to previous large studies, we identified leukocoria as the most common initial symptom, followed by strabismus. Also, the ratio of unilateral to bilateral disease were similar to those previously described in reports for developing countries. However, patient age at diagnosis tended to be relatively late, 32.7 and 22.8 months, for unilateral and bilateral cases, respectively. In Japan, patient age at diagnosis of unilateral and bilateral cases in 1976 was 34.8 and 15 months, and in 1992, 20.7 and 7.5 months, respectively, suggesting that increasing parental knowledge and advances in diagnostic modalities may result in earlier diagnosis. We found higher survival rate in patients who had less than 2 years of age at the time of diagnosis. Although compatible with some reports, this is in contrast with some previous studies reported that the earlier diagnostic age does not affect patient survival. This may also be accounted for lower survival of our patients.

Approximately 6% of patients with newly diagnosed retinoblastoma have a positive family history of the disease. In our study, 10 patients (7.2%) had a positive family history of retinoblastoma and we found a significantly

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higher survival rate in patients with positive familial history. This may reflect parental education and sibling and offspring screening as a cause of improvement in survival.

Enucleation was performed in 72.6% in our series. This is similar to the today trend, with approximately 65–75% of unilateral sporadic retinoblastoma managed with enucleation.21

Nowadays, extraocular retinoblastoma is rare in developed countries. In the United States, rate of extraocular retinoblastoma is 4.8–9.6%.22,23 The extraocular involvement in other studies from developing world were 19.9%,10 30%,11 29.4%,18 with overall survival rates of 89.6%, 80.9%, 85% respectively. We identified extraocular retinoblastoma in 51.5% of patients. Exoextraocular retinoblastoma has been identified as a factor for a very poor prognosis.24,25 Similarly our results showed that patients with stage II or more had a significantly less survival rate. This may be another reason for low survival rate in our study. The high rate of extraocular involvement as well as increase in the mean age at diagnosis emphasized the delayed diagnosis in our patients. The delay in diagnosis has been reported to associate the risk of local tumor invasion.26 In a study of 153 patients with retinoblastoma from Brazil the 3-year survival rate was 82% in the early diagnosis group (<6 months after symptom onset), compared with 44% in the late group (>6 months after symptom onset).27

Second neoplasms occur frequently in patients with hereditary (bilateral and familial unilateral) retinoblastoma. The cumulative incidence rate of developing second neoplasm in patients with heritable retinoblastoma is approximately 1% per year.28 Accordingly the duration of follow-up time is related to the rate of developing second neoplasm. There were no cases of a second neoplasm in our study. However, the survival rate of our patients with bilateral retinoblastoma was 62.6% at 10 years. The great discrepancy in survival rates in bilateral cases in our study compared to high survival rate in developed countries (more than 90%) may explain why no secondary neoplasm was found in our patients. Some patients who might have developed second neoplasms may have died beforehand.

**Conclusion**

We are aware of possible influence of environmental factors in etiology of non-heritable retinoblastoma.29,30 Unfortunately, we did not have reliable data concerning the socioeconomic condition and the kind of community (rural or urban) where the patients came from, but these issues should be evaluated in a prospective study. Small size of this series is another limitation that may affect the results. A larger study gathering the information from other referral centers in Iran with longer duration of follow-up is needed for definite conclusion.

As with all childhood cancers, it is essential that survivors of retinoblastoma should have long-term follow-up. Additional intraocular retinoblastoma may present several years after the first tumor, so, frequent ocular examinations under anesthesia even in unilateral retinoblastoma is a main part of this follow-up.4 This is particularly necessary in the case of heritable retinoblastoma because the mutant RB1 gene acts as a cancer susceptibility gene predisposing to the risk of a subsequent, histologically distinct cancer. Patients with hereditary retinoblastoma have approximately a 4% chance of developing a second cancer during the first 10 years of follow-up, 18% during the first 20 years, and 26% within 30 years.4 Consequently, in addition to the proper ocular examinations, systemic work up in accordance with pediatrician or oncologist is required.

Delay in the diagnosis and treatment may reflect the absence of known registry and counseling system. To evaluate incidence and survival of retinoblastoma patients in Iran and to ensure complete ascertainment and follow-up, the first step is to arrange a high quality national cancer registry system. Prompt referral of the suspected patients and appropriate education of the parents may help to achieve a better outcome.
References