Review of 20 Years’ Clinical Experience with Retinoblastomas in Southern Taiwan

I-Hui Yang, MD; Hsi-Kung Kuo, MD; Yung-Jen Chen, MD; Jong-Jer Lee, MD; Sue-Ann Lin, MD

Background: Retinoblastomas are the most common malignant intraocular tumor of childhood. We describe the survival outcomes and prognostic factors of patients with a retinoblastoma receiving primary treatment at our hospital over the last 20 years.

Methods: A retrospective series study of 30 retinoblastoma cases treated from January 1, 1987 to August 31, 2006 was conducted from a review of medical records and histopathological sections. Variables, including age at onset, laterality, treatment modalities, treatment delay, and optic nerve invasion, were analyzed to elucidate the prognostic factors associated with cumulative survival.

Results: Most of the cases had an advanced retinoblastoma, and 23 patients received enucleation treatment. The average period of delay for treatment was 5.37 months after discovery of the disease. The overall cumulative survival rate was 83.08%. Patients with optic nerve invasion had a significantly lower survival rate (60.0%) than those without optic nerve involvement (94.75%). Treatment delay in excess of 6 months was correlated with tumor invasion of the optic nerve.

Conclusions: Tumor invasion of the optic nerve is the most significant prognostic factor for surviving a retinoblastoma. Delayed treatment increases the risk of optic nerve invasion. Parental awareness of both the risk of this consequence and the significance of early treatment is vital to achieving improved survival rates.

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Key words: retinoblastoma, optic nerve invasion, survival analysis

Retinoblastomas are the most common malignant intraocular tumor of childhood, with a cumulative lifetime incidence of 1 in 18,000–30,000 live births worldwide. The disease results from loss or mutation of both alleles of the retinoblastoma gene, a tumor suppressor gene located on chromosome 13q14. The tumor most probably arises from either a precursor cone photoreceptor cell or a multipotent retinoblast. A century ago, retinoblastomas were nearly always fatal. Enucleation was the first method used to save an affected patient’s life. Later, external...
beam radiotherapy was employed to salvage the eye.\(^{3,4}\) Nowadays, the goal of treatment is not only to save lives but also to salvage vision, if possible, through focal methods, such as thermotherapy, cryotherapy, laser photocoagulation, and even plaque radiotherapy, which are sometimes used adjunctive to chemoreduction.\(^{5-10}\) In medically advanced countries,\(^{11-13}\) the prognosis for survival and preservation of vision in patients with a retinoblastoma has greatly improved over the past century due primarily to earlier detection of the disease as well as to these improved treatment methods. In underdeveloped countries, however, retinoblastomas are still associated with high mortality.\(^{14}\)

In this study, we report on 20 years of experience (January 1987 through August 2006) with retinoblastomas in a single medical center in southern Taiwan. The survival rate and associated prognostic factors were analyzed.

**METHODS**

In this retrospective study, the medical records of patients with a retinoblastoma receiving primary treatment from January 1987 to August 2006 at Kaohsiung Chang Gung Memorial Hospital were reviewed for analysis. In total, there were 30 patients undergoing primary treatment for retinoblastomas at our facility. These cases were included in the analysis of the cumulative survival rate and associated prognostic factors.

The collected data included age at onset, gender, laterality, family history, treatment modalities, and treatment delay. The age at onset was taken from the time the eye abnormality was noted by the family. The time interval between the age at onset and the age at initiation of treatment was defined as the treatment delay.

The available histopathological sections of the primary enucleated eyeballs were reviewed to determine retrolaminar tumor invasion of the optic nerve. In cases treated without enucleation, pretreatment computed tomographic or magnetic resonance images of the orbit were reviewed to assist judgment of grossly visible disease extension into the optic nerve and orbit. Optic nerve invasion in these patients was defined as marked thickening and enhancement of the optic nerve on the pretreatment imaging study of the orbit.

**Statistical analysis**

The Kaplan-Meier method was used to analyze the cumulative survival rate for all 30 patients. The effects of prognostic variables, including laterality, age at onset, optic nerve involvement, treatment delay, and treatment modality on the cumulative survival were initially evaluated with a log-rank test. Associations between the individual factors were estimated using Fisher’s exact test. The age at onset, laterality, optic nerve involvement, treatment delay, and treatment modality (having undergone enucleation or not) were further examined using a multivariate analysis with the Cox regression to determine the most important factors associated with the prognosis. The risk factors that correlated with optic nerve invasion by a retinoblastoma were evaluated with a binary logistic regression.

**RESULTS**

Our sample population consisted of 11 boys and 19 girls. Twenty-two of them were unilateral and 8 were bilateral cases. With regard to family histories, 25 were sporadic cases, 2 were familial with normal parents, and 3 were adopted with an unknown inborn family history.

The mean follow-up period for the 30 patients was 90.08 ± 55.12 months (2702.27 ± 1653.51 days), with a range of 1.8~186.9 months (54~5607 days). The respective onset, diagnosis, and treatment ages (mean ± SD months) for the various retinoblastoma groupings are listed in Table 1. For all patients, the interval (mean ± SD) between disease detection and diagnosis was 2.53 ± 4.29 months, while the interval between diagnosis and treatment was 2.83 ± 4.84 months; the interval between disease detection and treatment of 5.37 ± 5.93 months was defined as

**Table 1.** Mean Age of Onset, Diagnosis, and Treatment of Retinoblastomas in Various Groups

<table>
<thead>
<tr>
<th>Group</th>
<th>Age at onset (months)</th>
<th>Age at diagnosis (months)</th>
<th>Age at treatment (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unilateral (21)</td>
<td>20.71 ± 12.24</td>
<td>23.67 ± 10.71</td>
<td>25.95 ± 12.21</td>
</tr>
<tr>
<td>Bilateral (7)</td>
<td>11.57 ± 9.27</td>
<td>13.43 ± 10.28</td>
<td>18.00 ± 8.26</td>
</tr>
<tr>
<td>FH (2)</td>
<td>1.50 ± 0.71</td>
<td>2.00 ± 1.41</td>
<td>4.50 ± 4.95</td>
</tr>
<tr>
<td>Overall (30)</td>
<td>17.30 ± 12.44</td>
<td>19.83 ± 11.98</td>
<td>22.67 ± 12.39</td>
</tr>
</tbody>
</table>

**Abbreviation:** FH: patients with a family history of a retinoblastoma.
the treatment delay. The average age at onset for all patients was 17.30 months. Our sample was further stratified into groups according to the age at disease onset (< 18 months as early onset and ≥ 18 months as late onset) and the time period of post-onset therapy commencement (< 6 months as early and ≥ 6 months as delayed) for additional analyses.

The fundus drawings in the medical records most commonly showed an obscured fundus, total retinal detachment, or a large elevated whitish mass. Of the 22 unilateral cases, 21 eyes were graded as group V in the Reese-Ellsworth classification before treatment, with some even presenting with proptosis, while the remaining eye involving less-advanced disease was graded as group IIIb. In the 8 bilateral patients, 4 cases showed group V bilaterally, and 4 cases showed 1 eye with group V disease and the other eye with Ib, IIb, Ia, and IVb respectively. Thus, most of our cases displayed advanced disease before treatment.

Among the 22 patients with a unilateral retinoblastoma, 11 underwent enucleation, 8 had adjuvant radiation therapy and/or chemotherapy after enucleation, and 3 received non-surgical treatment (1 of them received only radiation therapy, the other 2 had both radiation and chemotherapy). Three patients died before the cutoff day, 2 of them received both radiation and chemotherapy as adjuvant management after enucleation, while the other had radiation and chemotherapy without enucleation. The retinoblastoma involved both eyes in 8 patients of this study. Half of them had non-surgical treatment (1 received radiation, 1 had chemotherapy, the other 2 had both radiation and chemotherapy), 3 underwent enucleation for the more severely affected eye in addition to adjuvant radiation therapy in 2 as well as laser therapy in 1 for the less-affected eye, and only 1 had bilateral enucleation. Two patients (50%) without enucleation died before the cutoff day (1 received chemotherapy only while the other had both radiation and chemotherapy). Most patients who experienced multiple modalities of therapy underwent enucleation as the initial treatment, and the adjuvant radiation and chemotherapy were administered variably according to optic nerve involvement and invasion of the resected end.

The overall cumulative survival rate after initial treatment, as determined by the Kaplan-Meier method was 83.08% (Fig. 1A). Five patients died before the cutoff date, and all of them died within 3 years after the initial treatment. Patients with a treatment delay of > 6 months and optic nerve invasion had a significantly lower survival rate (log-rank test, \( p = 0.039 \) and 0.011 respectively) than the others (Fig. 1B, C). The children who received enucleation of the diseased eye had a better survival rate (90.5% vs. 60.5%) than those that received radiation and/or chemotherapy only (Fig. 1D), but the difference was not statistically significant (\( p = 0.071 \)). Our data were unable to show an effect of other factors such as age at onset (\( p = 0.631 \)) or laterality (\( p = 0.373 \)) on survival by the log-rank test. A treatment delay of > 6 months was associated with optic nerve invasion of the tumor (Fisher’s exact test, \( p = 0.045 \)), however, no significant association between other pairs of factors was revealed by our analysis. Optic nerve invasion was further demonstrated to be the most important risk factor associated with mortality (\( p = 0.040, \) hazard ratio = 10.03) from the Cox regression with a backward elimination method (Table 2).

Treatment delay exceeding 6 months was further identified as a risk factor for optic nerve invasion (binary logistic regression with backward elimination, \( p = 0.024, \) odds ratio = 7.00). The effects of other factors, regardless of the significance, are listed in Table 3.

**DISCUSSION**

The survival rate with a retinoblastoma has been reported to be near 90% in developed countries.\(^{11-13}\) However, in a series of 96 cases in northern Taiwan from 1978 to 2000, the 3-year cumulative survival rate was only 64.41%. Reluctance to accept treatment promptly after a diagnosis of the disease and turning to herbal or traditional therapy were regarded as the major causes of the poor prognosis.\(^{11-13}\) The relatively higher survival rate in this study may be ascribed to 2 reasons. First, parents of children may hesitate to treat the disease and seek a second, third, or further opinions in a variety of hospitals. During the period of hesitance, the disease usually progresses to a very advanced stage, after which the children need to receive therapy in better-equipped medical facilities in northern Taiwan. This is supported by a report\(^{15}\) with a high ratio (33 of 96) of very advanced orbit-involving retinoblastomas, which was rarely seen in our cases. This point of view is
also supported by the fact that the number of patients who received primary treatment in our hospital was much smaller than that in northern Taiwan during a similar time period. Second, data were collected in this study from 1987 to 2006. During the most recent 12 years, government-sponsored health insurance, which has been in place since 1995 and which covers at least 90% of the cost of treatment, may have encouraged parents to accept proper medical treatment. Despite the small progress in the cumulative survival to 83.08%, it is still much lower than those reported in analogous Western and Japanese studies.

Optic nerve involvement has long been recognized as a risk factor for tumor metastasis as well as a poor prognosis, with mortality increasing with the extent of optic nerve involvement. In our study, optic nerve invasion was a statistically significant factor for low survival. Patients without optic nerve involvement had a survival rate of 94.75%, whereas those with optic nerve invasion had a survival rate of 60.00%.

**Fig. 1** Kaplan-Meier curves for survival of patients with a retinoblastoma. Survival time was measured from initiation of treatment to the date of either death or the last follow-up. The log-rank test was used to compare various conditions of patients. (A) The survival curve of all 30 patients was 83.08%. (B) Patients with delayed treatment exceeding 6 months had a significantly lower survival rate (66.67%) than those (94.12%) treated within 6 months. (C) Optic nerve invasion resulted in a significantly lower survival rate (60.00%) than those without it (94.75%). (D) Enucleation was associated with a higher survival rate (90.5%) than for patients without surgical treatment (60.5%).
Table 2. Relative Effects by Prognostic Factors of Predicting Survival of Patients with Retinoblastoma

<table>
<thead>
<tr>
<th>Factor</th>
<th>No. of cases (%)</th>
<th>Hazard ratio (95% confidence interval)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilateral tumor</td>
<td>8 (27%)</td>
<td>1.98 (0.30~12.83)</td>
<td>0.475</td>
</tr>
<tr>
<td>Enucleation</td>
<td>22 (73%)</td>
<td>0.67 (0.07~5.99)</td>
<td>0.717</td>
</tr>
<tr>
<td>Late onset (≥ 18 months of age)</td>
<td>15 (50%)</td>
<td>2.14 (0.20~22.60)</td>
<td>0.526</td>
</tr>
<tr>
<td>Treatment delay (≥ 6 months)</td>
<td>12 (40%)</td>
<td>3.84 (0.39~38.07)</td>
<td>0.251</td>
</tr>
<tr>
<td>Optic nerve invasion</td>
<td>10 (33%)</td>
<td>10.03 (1.12~90.15)</td>
<td>0.040</td>
</tr>
</tbody>
</table>

Table 3. Relative Effects of Factors on Tumor Invasion of the Optic Nerve with Retinoblastoma

<table>
<thead>
<tr>
<th>Factor</th>
<th>No. of cases (%)</th>
<th>Odds ratio (95% confidence interval)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilateral tumor</td>
<td>8 (27%)</td>
<td>0.37 (0.05~2.92)</td>
<td>0.343</td>
</tr>
<tr>
<td>Enucleation</td>
<td>22 (73%)</td>
<td>0.24 (0.03~2.05)</td>
<td>0.193</td>
</tr>
<tr>
<td>Late onset (≥ 18 months of age)</td>
<td>15 (50%)</td>
<td>2.98 (0.40~22.09)</td>
<td>0.285</td>
</tr>
<tr>
<td>Male gender</td>
<td>11 (37%)</td>
<td>0.49 (0.06~4.08)</td>
<td>0.510</td>
</tr>
<tr>
<td>Treatment delay (≥ 6 months)</td>
<td>12 (40%)</td>
<td>7.00 (1.29~37.91)</td>
<td>0.024</td>
</tr>
</tbody>
</table>

Invasion had a 94.75% survival rate compared to only 60% for those with such encroachment. It was also the only significant factor predicting survival in the multivariate Cox regression. However, the effect of the other factor, such as treatment delay, on survival may have been masked in the regression due to its high correlation with optic nerve invasion. Further analysis showed that a delay in treatment of the disease was associated with a higher risk of optic nerve involvement, and this, therefore, may have indirectly decreased the survival of patients. Nevertheless, the effect of other factors on the prognosis of the disease might not have been demonstrated in this study because of the insufficient discriminative power of the statistics (14% for bilateral tumors, 13% for enucleation, 31% for late onset, and 63% for treatment delay) due to the small number of cases. Similarly, associations between optic nerve invasion by the tumor and factors of bilateral tumor, enucleation, late onset of disease, and gender (with powers in the logistic regression of 14%, 30%, 29%, and 12%, respectively) might not have been clearly explicated due to the low case number.

The trend that age at onset demonstrated in our patient series was similar to previous findings. The age at diagnosis in a literature review ranged 20.7~30.96 months in unilateral cases, and 7.5~18.87 months in bilateral cases,\textsuperscript{12,15,18,19} with the variation presumably due to differences in era, data collection, and countries. Diagnosis at an older age appears to be a common finding in studies from developing countries. In the present study, delays of 2.53 and 2.83 months were demonstrated from first detection to subsequent formal diagnosis of the disease, and from diagnosis to commencement of treatment, respectively, with a total elapsed time of 5.37 months from detection to treatment indicating a relative lack of awareness and poor compliance by Taiwanese families. From the log-rank analysis, a treatment delay of 6 months was significantly associated with survival, with a survival rate of 94.12% for early treatment (< 6 months) compared to only 66.67% for later intervention (≥ 6 months). This trend is compatible with the results of a previous study.\textsuperscript{20} Although treatment delay was not disclosed to be a significant predictor of poor survival because of the masking effect of optic nerve invasion and the low discriminative power due to the small number of cases, it might be reasonable to suggest that the cumulative delay may have resulted in greater advancement of disease at presentation and before treatment, limiting the opportunity for more-conservative interventions, increasing the likelihood of poor outcomes, and reducing the survival rate. Therefore, delayed treatment appears to be the main cause of the poor survival rate in our area, and thus the main issue we must face in clinical practice.

Management of retinoblastomas is highly individualized.\textsuperscript{21,22} In our sample population, treatment varied widely due to the disease severity and compliance issues; therefore, treatment modalities were not investigated in the outcome evaluation. Although there has been an increase in the use of alternative eye- and vision-conserving therapies, primary enucleation continues to be the choice for advanced
intraocular retinoblastomas. Primary focal measures are mainly reserved for small tumors.\(^{(23)}\) The evolution of chemoreduction has greatly improved ocular salvage rates in Reese-Ellsworth group I, II, and III cases. For Reese-Ellsworth group V eyes, however, there has been only limited improvement, with a globe salvage rate of about 50\%.\(^{(24)}\) The more advanced the disease is, the more aggressive the treatment modalities that are required. In our study, only 5 eyes had a less-advanced form of the disease. As most of our cases involved advanced retinoblastomas (Reese-Ellsworth group V), enucleation was the most common intervention. Although this is currently not the foremost treatment, it still plays a major role in saving lives with advanced disease. With the development of chemoreduction, this modern treatment option should be considered for selected cases as it conserves the globe. This, in turn, should encourage more parents to consent to earlier treatment, ultimately saving more young lives.

From a literature review, the histopathological factors indicative of a poor prognosis included choroidal infiltration, retrolaminar optic nerve invasion, invasion of the resected end of the optic nerve, scleral infiltration, and extrascleral extension.\(^{(23)}\) In our enucleated patients, however, scleral infiltration and extrascleral extension were not noted. Further, statistically significant relationships were not demonstrated in the survival analysis for choroidal invasion or retrolaminar optic nerve invasion with a free resected end (data not shown). Resection of the optic nerve was inadequate in 5 cases, with 2 of them suffering poor outcomes. One of the pair refused further radiotherapy until a retinoblastoma of the orbit recurred 6 months later. Unfortunately, further chemotherapy for that later-developing distant metastasis did not reverse the disease progression, and the patient died. The other patient had adjuvant chemotherapy and radiotherapy after enucleation but died of a systemic fungal infection with sepsis which developed during the treatment course. Although the efficacy of adjuvant therapy is controversial for retinoblastomas, adjuvant therapy is generally administered in cases with high-risk histopathological characteristics.\(^{(23)}\)

In conclusion, most of our patients initially presented with advanced disease and had postponed professional consultation until further progression developed, with a 5.37-month delay between first detection and subsequent treatment. In our analysis, a 6-month treatment delay was significantly related to optic nerve invasion, which appeared to lead to poor outcomes. Despite the fact that modern medicine is readily available in Taiwan, delays in detection and poor compliance are revealed as the main causes of treatment failure in this study. Enucleation remains the mainstay of treatment for advanced retinoblastomas; however, chemoreduction should be considered in selected cases. Therefore, education of parents appears to be the best way to resolve the problem of delayed treatment, thereby improving the rates of survival, globe sparing, and even vision salvage in children with a retinoblastoma.

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**REFERENCES**

10. Sussman DA, Escalona-Benz E, Benz MS, Hayden BC,


視網膜胚細胞瘤之臨床治療—南台灣二十年經驗之回顧

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背 景：視網膜胚細胞瘤是幼童最常見的眼內原發惡性腫瘤。本文回顧過去二十年來 (1987-2006) 於本院接受治療之經驗，藉以了解影響疾病預後及病患存活的重要因子。

方 法：以查閱病歷及病理切片的回溯性研究方式取得臨床資料，進而分析患者發病年齡、單雙側、治療方法、治療延誤的時間長短等因素，對於治療後存活率及腫瘤侵犯視神經的影響。

結 果：總數有 30 位患者，大部分都是較嚴重的視網膜胚細胞瘤，主要接受眼球摘除的手術治療。發現病徵後平均延誤 5.37 個月後才接受治療，整體存活率是 83.08%，但有視神經侵犯者是 60.00%，顯著的低於無視神經侵犯者 (94.75%)，而延誤治療超過 6 個月是視神經侵犯最重要的因子。

結 論：視神經侵犯將造成視網膜胚細胞瘤不良的預後，眼科醫師應告知患者親人延誤治療時機將增加視神經侵犯的機會並影響病患存活。

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關鍵詞：視網膜胚細胞瘤，視神經侵犯，存活率分析