Prognostic Factors in Retinoblastoma

Arun D. Singh, MD; Carol L. Shields, MD; and Jerry A. Shields, MD

INTRODUCTION

Retinoblastoma is the most common primary intraocular malignant tumor in children with an incidence of 1 in 15,000 live births. The average annual incidence of retinoblastoma in the United States has been estimated at 10.9 per million for children <5 years, and the incidence has remained stable from 1974 to 1985. Most children present with a white pupillary reflex or leukocoria. Ancillary studies such as ultrasonography, computed tomography, and magnetic resonance imaging can assist in confirming the diagnosis.

In recent years, there has been a trend away from enucleation and an increase in the use of alternative globe-conserving methods of treatment including external beam radiotherapy, plaque radiotherapy, laser photocoagulation, cryotherapy, and trans-pupillary thermotherapy. Currently, chemotherapy is being used increasingly as chemoreduction with other adjuvant therapy to avoid external beam radiotherapy and enucleation. Recent advances in the treatment of retinoblastoma have led to a reduced risk of metastasis and improved survival rates in developed countries. Five-year survival rates of 91%, 93%, and 88% have been reported from the United States, Japan, and the United Kingdom, respectively. However, in underdeveloped countries, retinoblastoma is still associated with high mortality. Of 44 Nigerian patients with retinoblastoma, 57% (25 patients) had a fatal outcome.

Retinoblastoma is a familial disorder with an autosomal dominant inheritance. Approximately 60% of patients are considered sporadic and 40% are heritable. Of the heritable type of retinoblastoma, 5%-15% have an existing family history and the remaining 25% are due to new germline mutations. The heritable variant of retinoblastoma tends to be bilateral and presents earlier with a mean age of 12 months. The sporadic type of retinoblastoma tends to be unilateral and presents later with a

EDUCATIONAL OBJECTIVES

1. To review clinical and histopathologic prognostic factors that influence survival in retinoblastoma.
2. To discuss the delay in diagnosis, intraocular surgery, and use of external beam radiotherapy and how they significantly influence the survival in retinoblastoma.
3. To determine the importance of careful histopathologic evaluation of the enucleated globe as it may influence the decision to use prophylactic chemotherapy.

See quiz on page 168; no payment required.
mean age of 24 months. All bilateral cases are considered heritable and harbor germline mutation. In addition, approximately 15% of all unilateral cases are also heritable. Patients with the heritable variant of retinoblastoma are particularly susceptible to the development of pineoblastoma and other second malignant neoplasms, particularly osteosarcoma.

Metastatic disease at the time of retinoblastoma diagnosis is rare. Therefore, staging procedures such as bone scans, lumbar puncture, and bone marrow aspirations at initial presentation are not recommended.16,17 The metastasis in retinoblastoma usually occurs within 1 year of diagnosis of retinoblastoma. If there is no metastatic disease within 5 years of retinoblastoma diagnosis, the child is considered cured.18 Involvement of the central nervous system and hematogenous spread are common. Survival with metastatic retinoblastoma is limited, with death occurring generally within 6 months.19,20

This review provides an update on the prognostic factors that may influence decisions regarding the use of adjuvant therapy in high-risk cases of retinoblastoma. The prognosis can be related to clinical features such as delay in diagnosis, prior intraocular surgery, and the genetic subtype of retinoblastoma (Table 1). Treatment factors that can affect prognosis include use of external beam radiotherapy and chemoreduction. Tumor histopathologic factors include tumor invasion of the choroid, optic nerve, and orbit.

**PROGNOSTIC FACTORS**

**Clinical Prognostic Factors**

*Delay in Diagnosis.* The most common presentations of retinoblastoma include leukocoria and strabismus.20 Children presenting with such symptoms or signs should be examined by an ophthalmologist to exclude retinoblastoma. In a study of 100 patients with retinoblastoma in the United Kingdom, a delay in diagnosis did not increase the likelihood of treatment by enucleation, but the risk of local tumor invasion was increased.21 The impact of such a delay on survival is unknown.

In another study of 153 children with retinoblastoma from Brazil, 80 (52%) patients received treatment within 6 months symptom onset (early diagnosis) and 73 (48%) received treatment >6 months after symptom onset (late diagnosis). The 3-year survival rate was 82% in the early diagnosis group compared with 44% in the late diagnosis group. The worse prognosis in the late diagnosis group correlated with the tendency of patients in this group to exhibit extraocular extension of the retinoblastoma.22,23

*Prior Intraocular Surgery.* Extraocular spread of retinoblastoma is a poor prognostic factor. Intraocular surgical procedures such as pars plana vitrectomy, inadvertently performed on patients with retinoblastoma, predisposes to orbital extension or metastasis of retinoblastoma. Stevenson et al24 reported three such patients, all of whom developed orbital retinoblastoma following intraocular surgery. Shields et al25 reported a series of 11 patients after vitrectomy. Each child was treated by prompt enucleation and most received adjuvant prophylactic orbital radiotherapy and chemotherapy. Metastasis developed in one case with a mean follow-up of 83 months.

*Genetic Subtype.* The heritable form of retinoblastoma has significant long-term prognostic implications. Second malignant neoplasms, which occur predominantly in the heritable form of retinoblastoma, have now become significant contributors to overall mortality.26 In a large study from the United Kingdom, the overall 3-year survival rate was 88% in 431 patients with retinoblastoma who underwent follow-up for up to 17 years.26 Patients with bilateral tumors had worse long-term survival rates because of later deaths from second primary neoplasms.5

Similar results were observed in a study from Japan.19 In 1147 cases of retinoblastoma from the National Registry of Retinoblastoma of Japan, the 5-year survival rate of 93% for 757 unilateral cases

**TABLE 1**

<table>
<thead>
<tr>
<th>Poor Prognostic Factors in Retinoblastoma</th>
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<tr>
<td><strong>Clinical</strong></td>
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<td>Delay in diagnosis (&gt; 6 mo)21-23</td>
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<td>Prior intraocular surgery24,25</td>
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<td>Use of external beam radiotherapy27,31,32,34</td>
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<td>Optic nerve invasion</td>
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<td>Retrolaminar invasion23,44,45,52</td>
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<td>Invasion up to the line of transection23,45,52</td>
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<td>Orbital invasion18,44</td>
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was similar to that of 92% for 390 bilateral cases. However, the 10-year survival rates were 92.3% and 86.7% for the unilateral and bilateral cases, respectively. The occurrence of a second neoplasm was the main cause of death in the hereditary cases 10 years after diagnosis.13

Second Malignant Neoplasms

It is now recognized that more children with retinoblastoma die from the second malignant neoplasm than from the retinoblastoma itself.27 The incidence of second malignant neoplasm in the heritable form of retinoblastoma has been reported to be between 5% and 90% in various studies due to differences in the methods of ascertainment of the cases and analysis of the data (Table 2).27 In a study from the United Kingdom, Draper et al28 reported a cumulative incidence rate of 8% after 18 years in 384 cases with the heritable form of retinoblastoma. Roarty et al29 using the life table method, calculated cumulative incidence in 215 patients with bilateral retinoblastoma to be 18% at 20 years. Using Kaplan-Meier analysis, Mohney et al30 estimated the incidence of second malignant neoplasm in 82 patients with heritable retinoblastoma as 16% at 25 years and 30% at 40 years. In a detailed study of 1604 patients with retinoblastoma, of whom 961 had hereditary retinoblastoma, the cumulative incidence (Kaplan-Meier estimates) of second malignant neoplasms, 50 years after diagnosis of hereditary retinoblastoma, was 10 times higher in hereditary cases versus nonhereditary cases (51% versus 5%) (Figure 1).31,32 It is estimated that the cumulative incidence rate of developing second malignant neoplasm in heritable retinoblastoma is approximately 1% per year.32

There are many types of second malignant neoplasms, and at least 35 distinct types have been reported in association with retinoblastoma.33 The majority of the neoplasms are osteosarcoma (37%) and soft-tissue sarcoma (7%).34 Cutaneous melanoma represents approximately 7% of all second malignant neoplasms.34 The risk of developing bone tumors and connective and soft-tissue tumors in heritable retinoblastoma is increased approximately 400 times and 100 times, respectively, compared with the normal population.32 The role of radiotherapy in the pathogenesis of second malignant neoplasm is discussed below.

Trilateral Retinoblastoma

The association between heritable retinoblastoma and a primary intracranial malignancy especially of the pineal gland is termed trilateral retinoblastoma.35 In patients with bilateral retinoblastoma, the presence of an intracranial malignan-
Incidence is now recognized to be the most frequent cause of death in the first decade of life, accounting for 50% of all deaths.\textsuperscript{36}

Trilateral retinoblastoma occurs in approximately 8% of all heritable retinoblastoma.\textsuperscript{37} The nature of primary intracranial malignant tumor can vary in its location and histopathologic features.\textsuperscript{5} The majority of tumors are located in the pineal region but can also occur in the suprasellar and parasellar regions.\textsuperscript{38,39} The overall prognosis in the presence of trilateral retinoblastoma is poor.\textsuperscript{40} Kivela\textsuperscript{41} reported findings of a meta-analysis based on all published reports of trilateral retinoblastoma between 1966 and 1998. Data on 106 children were analyzed. The median time from retinoblastoma to the diagnosis of intracranial tumor was 21 months with 75% of intracranial tumor cases diagnosed within 1 year of retinoblastoma diagnosis. Screening by neuroimaging was able to detect intracranial tumor at an earlier age but did not prolong survival. The median survival time after diagnosis of trilateral retinoblastoma was 9 months.\textsuperscript{41} It is hoped that earlier neuroimaging studies may detect the intracranial tumor and allow earlier treatment.

**External Beam Radiotherapy.** The relationship between radiation and second malignant neoplasms is complex.\textsuperscript{27} At least two effects of external beam radiotherapy in the pathogenesis of second malignant neoplasms in patients with retinoblastoma have been identified. These include enhancement of the baseline risk and a localizing effect.\textsuperscript{31} The effects of radiotherapy are influenced by the age of the recipient and are believed to be dose dependent.\textsuperscript{31,32}

The previously mentioned risk of developing second malignant neoplasms is doubled by the use of external beam radiotherapy.\textsuperscript{31,32} In the study of 1604 patients with retinoblastoma previously described, the cumulative incidence (Kaplan-Meier estimates) of second malignant neoplasms without radiation progressively increased from 3% at age 10 years to 9% at age 30 years (Figure 2). With longer follow-up of 50 years after diagnosis of retinoblastoma, the incidence more than doubled in cases that were treated with external beam radiotherapy when compared with those not receiving radiotherapy (58% and 27%, respectively).\textsuperscript{31}

The influence of radiotherapy in causing second malignant neoplasm appears to be dependent on the age of the child, when radiotherapy is administered, and the dose of radiation applied.\textsuperscript{31,32} If radiation is given to children who are <1 year of age, the cumulative incidence of a second malignant neoplasm is 9% at age 10 years and 34% at 30 years compared to 5% and 22%, respectively, for children who are >1 year when treated.\textsuperscript{31} In addition, the effect of radiotherapy may be dose dependent with elevated risk associated with doses >50 Gy.\textsuperscript{32} Currently, with megavoltage techniques, an average dose of 44 Gy is used to treat retinoblastoma, and the high-energy photon beams deliver a uniform dose to the bone and soft tissues.\textsuperscript{6} With present techniques of external beam radiotherapy for retinoblastoma, the enhancing influence of external beam radiotherapy in the pathogenesis of second malignant neoplasm may be lower than the published data.

**Use of Chemoreduction.** Chemoreduction involves the administration of chemotherapy for advanced intraocular retinoblastoma to achieve tumor reduction so that focal ophthalmic therapy can be applied to par-
<table>
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<tr>
<th>Study</th>
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<td>Messmer et al</td>
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<td>Late enucleation*; retrolaminar optic nerve invasion; optic nerve up to resection line; choroidal invasion</td>
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<tr>
<td>Magrann et al</td>
<td>1922-1986</td>
<td>240</td>
<td>Age; extent of optic nerve invasion; choroidal invasion</td>
<td>Scleral invasion; laterality</td>
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* =>120 days after the initial presentation.

Histopathologic Prognostic Factors

Many studies have evaluated the histopathologic prognostic factors including tumor size, tumor growth pattern, tumor differentiation, extension into the choroid, optic nerve, anterior chamber, and extrascleral tissues. Multivariate analysis, in which correction for confounding effects of multiple risk factors is made, is particularly helpful in identifying the influence of individual prognostic factors (Table 3).

Tumor parameters such as size, growth pattern (endophytic or exophytic), and differentiation do not significantly influence the systemic prognosis. The Reese-Ellsworth classification traditionally has been used to grade the retinoblastoma from stage I to stage V. The classification system is based on the number, size, and location of the tumors. The Reese-Ellsworth stage of retinoblastoma indicates the prognosis for globe conservation rather than systemic prognosis due to metastatic disease. The pattern of tumor growth (endophytic or exophytic) has no significant influence on the prognosis. In a retrospective review of 297 cases of enucleated and histologically proven unilateral retinoblastoma, endophytic retinoblastoma (181 cases) was found more often than exophytic retinoblastoma (116 cases). With a 5-year minimum follow-up, the clinical appearance of either endophytic or exophytic tumor did not correlate with the optic nerve invasion, orbital recurrence, or survival of the patient. A similar lack of significant influence of tumor differentiation on systemic prognosis has been observed.

Choroidal Invasion. There are conflicting results as to whether extension of retinoblastoma into the choroid is a poor prognostic factor. A histopathologic review of 74 patients with retinoblastoma revealed choroidal invasion correlated with 100% survival provided the sclera, iris, and optic nerve were not involved. In a multivariate analysis of risk factors for metastasis in retinoblastoma treat-
ed by enucleation, statistical analysis of 361 cases indicated histologic detection of choroidal invasion was not significantly associated with a fatal outcome. In a detailed study of metastatic potential of choroidal invasion of retinoblastoma, clinical and histopathologic data were evaluated on 289 eyes enucleated for retinoblastoma. Sixty-seven (23%) eyes had histopathologic evidence of choroidal invasion. Patients with choroidal invasion were more likely to develop metastasis than those without choroidal invasion (P=.0001). When patients with optic nerve invasion were excluded, there was no significant risk, but there was a trend toward the development of metastasis (P=.10). The choroidal invasion could be predicted by iris neovascularization. The authors concluded choroidal invasion of retinoblastoma is a risk for metastasis, especially if it is associated with any degree of optic nerve invasion. Studies using methods of multivariate analysis have supported the view that choroidal invasion by retinoblastoma increases the risk of metastatic disease.

Optic Nerve Invasion. Optic nerve invasion of retinoblastoma is a poor prognostic factor for patients with retinoblastoma. In fact, multivariate statistical analysis has indicated histologic detection of optic nerve invasion by retinoblastoma is one of the most highly predictive factors for death from retinoblastoma. Since 1960, the frequency and severity of optic nerve invasion has been less extensive due to the earlier diagnosis of retinoblastoma.

Optic nerve invasion is present in approximately one third of enucleated globes for retinoblastoma and correlates with the presence of choroidal or scleral extension. Optic nerve invasion is categorized as prelaminar, laminar, postlaminar, and up to the line of transection. Prelaminar optic nerve involvement is most common, representing about half of all cases of optic nerve involvement. The laminar and the retrolaminar involvement in equal portions accounts for the remaining half of the cases. In our experience, optic nerve involvement up to the line of transection is rare and was seen in 2 (1%) of 289 cases.

There is increasing mortality with increasing extent of optic nerve involvement. However, it is generally agreed that prelaminar involvement of the optic nerve does not increase the risk of metastasis. The impact of laminar involvement on metastasis is debated. Retrolaminar involvement is a poor prognostic factor, and optic nerve invasion by retinoblastoma up to the line of transection predicts the worst prognosis. In a study of 361 cases, the multivariate odds ratio for metastasis was 9 when the optic nerve was involved up to the resection line compared to 4 when the retinoblastoma extended retrolaminar but did not extend up to the resection line.

In another study of 172 patients with retinoblastoma, the 3-year disease-free survival rate was 97% when the optic nerve was not involved compared to 55% when the optic nerve invasion was up to the line of transection. The prognosis was intermediate with retrolaminar involvement. Further analysis of 149 patients, after excluding those with extrascleral extension and optic nerve involvement up to the resection line, revealed retrolaminar involvement of the optic nerve was a significant prognostic factor for metastasis. Similar prognostic implications of retrolaminar invasion of the optic nerve by retinoblastoma have been supported by other studies.

Optic nerve invasion can be predicted by the presence of a large exophytic retinoblastoma with secondary glaucoma and vitreous hemorrhage. These findings should alert the clinician to suspect optic nerve invasion. When enucleation is performed for retinoblastoma, an attempt should be made to salvage a long stump of optic nerve (10-15 mm) so as to transect the optic nerve beyond the extent of involvement by retinoblastoma.

Orbital Invasion. Extradural or orbital extension of retinoblastoma is possibly the worst prognostic factor for death from retinoblastoma. The multivariate odds ratio of 27 for metastasis is highest when there is invasion into the orbit indicating that orbital invasion is the worst prognostic indicator in retinoblastoma with up to 90% mortality in 2 years. The presence of orbital invasion of retinoblastoma is associated with a 10 times greater risk of metastasis compared to cases with no orbital invasion.

Prophylactic chemotherapy with adjuvant orbital radiotherapy has been advocated in retinoblastoma cases with poor prognostic indicators such as prior intraocular surgery, orbital extension of retinoblastoma, and anterior chamber seeding, as well as in cases with extension of retinoblastoma up to the line of optic nerve transection. The role
of such prophylactic treatment in instances with isolated chorioidal invasion and retrolaminar optic nerve invasion remains controversial.65

In a recent retrospective study, outcome was analyzed in 80 unilateral cases treated by primary enucleation with histopathologic risk factors for metastasis. The presence or absence of metastasis at a minimum of 12 months follow-up was the main outcome measure. Forty-six patients were treated by prophylactic chemotherapy (treated group) for at least 6 months and 34 patients were untreated. A significant difference (P<0.01) was found in the incidence of metastasis between the treated (2.4%) of 46 and the untreated (8.2%) of 34 groups.57 Our data suggest beneficial effects of prophylactic therapy in reducing the risk of metastatic disease in a select group of high-risk retinoblastoma.

CONCLUSION

Various clinical and histopathologic prognostic factors have been identified in retinoblastoma. Early recognition of symptoms with a high index of suspicion and prompt referral to a specialized center will further improve survival in patients with retinoblastoma. Patients with germline mutations of retinoblastoma gene are at risk for development of pineoblastoma and other second malignant neoplasms. The use of external beam radiotherapy enhances the risk for development of second malignant neoplasms. Uncontrolled clinical studies suggest the use of prophylactic chemotherapy in high-risk retinoblastoma patients is effective in reducing the risk of metastasis. Due to the limited number of cases treated at a given center, there is a need for a collaborative prospective randomized clinical trial evaluating the efficacy of prophylactic chemotherapy in retinoblastoma patients with poor prognostic factors.

REFERENCES

33. Dunkel IJ, Gerald WL, Rosenfield NS, et al. Outcome of patients