

Outcome of Children With Retinoblastoma and Isolated Choroidal Invasion

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Objectives: To evaluate the outcome of children with different degrees of choroidal invasion, to compare different systems for grading the extent of choroidal invasion, and to assess the role of concomitant prelaminar optic nerve and anterior segment invasion as predictors of extraocular relapse.

Design: Retrospective analysis of children included in 4 prospective protocols (January 1, 1989, through June 31, 2010). Children with postlaminar optic nerve or scleral involvement and overt extraocular disease were excluded. Adjuvant chemotherapy was not scheduled. All slides were reviewed, and massive involvement was classified according to 3 definitions: (1) extending at least 3 mm in any dimension, (2) through the choroid's whole thickness, and (3) more than 50% of the thickness and/or more than 1 cluster.

Results: One hundred sixty-seven children (35 with massive invasion) were studied (136 did not receive adjuvant

therapy). The probability of 5-year event-free survival was 98.1% and the probability of overall survival was 98.7% because 1 patient relapsed. Children with massive invasion had a significantly lower event-free survival probability (94.2%) compared with those with focal invasion (99.2%) ($P=.04$). However, no significant difference was found in overall survival probability (98.7% vs 99.2%; $P=.29$). No significant effect of other risk factors was found.

Conclusions: Survival was excellent without adjuvant therapy, and no other factors correlated with survival. Children with massive invasion have a higher relapse rate but comparable survival to those with focal invasion provided that aggressive therapy for extraocular relapse is available with adequate safety conditions.

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RETINOBLASTOMA IS A HIGHLY curable neoplasm in developed countries, mostly because it is usually diagnosed when it is confined to the retina. Enucleation cures most cases of unilateral disease, and survival is not jeopardized by conservative therapy in children with bilateral tumors. Extraocular dissemination is therefore uncommon, and disease-free survival rates approach 100%.¹ The few patients who experience extraocular relapse after enucleation have risk factors discovered during the pathologic examination of the enucleated eye, such as invasion to the postlaminar optic nerve, the choroid, or the sclera.² However, the information for estimating the role of some of these risk factors, especially choroidal invasion, as predictors of extraocular relapse comes mostly from historical reports that involve patients treated with different indications for adjuvant therapy³⁻¹² (**Table 1**).

On the basis of that limited evidence, many treatment groups accept that mas-

sive invasion of the choroid is a significant risk factor for extraocular relapse, justifying the use of adjuvant chemotherapy in an attempt to prevent it.⁶ However, the definition of massive invasion and the processing of enucleated eyes in different centers are variable, so no comparison or pooled analysis can be made among different treatment groups.¹³ Therefore, the natural history of children presenting with isolated choroidal invasion remains largely unknown. However, currently, after consensus about the terms used for grading choroidal invasion and the procedures for processing enucleated eyes, some of these limitations have been overcome and valuable data may become available.¹⁴ The analysis of an adequate population of patients often treated in prospective protocols is now possible with the emergence of large treatment groups in developing countries. At our institution, children with isolated choroidal invasion have been treated according to prospective protocols without adjuvant chemotherapy for more than 20 years.¹⁵⁻¹⁷ The outcome of

Table 1. Reported Studies on Choroidal Invasion in Retinoblastoma

Source	Study Design (Dates)	No. of Patients With Isolated Choroidal Invasion	No. of Patients With Isolated Massive Choroidal Invasion	Treatment	Outcome	Comments
Uusitalo et al, ⁴ 2001	Retrospective (1977-1998)	37	8	No adjuvant therapy	No events	The authors concluded that chemotherapy is not needed
Shields et al, ⁵ 1993	Retrospective (1974-1991)	37	Not reported	Not reported	3 Patients had extraocular relapse	No statistically significant increased risk for extraocular relapse for patients without concomitant optic nerve invasion
Honavar et al, ⁶ 2002	Retrospective (1974-1999)	Not reported	8	6 observation, 2 adjuvant therapy	No events	
Howarth et al, ⁷ 1980	Prospective (1970-1977)	21	Not reported	Adjuvant chemotherapy	No events	
Khelifaoui et al, ⁸ 1996	Retrospective (1977-1990)	73 ^a	Not reported		3 Events (2 orbital relapse), 1 death	Significant factor in multivariate analysis
Stannard et al, ⁹ 1979	Retrospective (1952-1975)	12	5	Not reported	No events	
Gupta et al, ¹⁰ 2009	Retrospective (1996-2000)	57 ^a	39	Not reported	No events in isolated choroidal invasion	
Kopelman et al, ¹¹ 1987	Retrospective (1922-1959)	118 ^a	Not reported	Not reported	39% Mortality	Lost significance in multivariate analysis
Rubin et al, ¹² 1985	Retrospective (1958-1983)	14	Not reported	Not reported	81% Mortality	Lost significance in multivariate analysis

^aPatients with massive choroidal invasion and other concomitant risk factors, such as postlaminar optic nerve invasion or microscopic scleral invasion, are included.

children with choroidal invasion in each protocol was published, but relatively few patients were included in each study; thus, a combined analysis makes it possible to determine its natural history in a larger cohort, using the current consensus definitions. Therefore, in this context, the current study was performed to investigate the following issues: (1) the outcome of children with isolated choroidal invasion treated only with enucleation, (2) the outcome of children with different degrees of choroidal invasion, (3) the comparative value of different systems for grading the extent of choroidal invasion in enucleated eyes to predict the extraocular relapse rate, and (4) the role of other concomitant disease risk factors, such as prelaminar optic nerve and anterior segment invasion, as predictors for extraocular relapse.

METHODS

The clinical records of all patients with isolated choroidal invasion seen at our institution and included in 4 successive institutional review board–approved prospective protocols from January 1, 1989, through June 31, 2010, were retrospectively analyzed. Inclusion criteria for this study were as follows: isolated choroidal invasion on pathologic examination, defined as that occurring with any degree of invasion to the choroid

without concomitant scleral or retrolaminar optic nerve involvement, and absence of overt extraocular disease at diagnosis, including the orbit or distant metastatic sites.

Patients underwent routine computed tomography or magnetic resonance imaging of the head and orbit at diagnosis, but bone marrow and cerebrospinal examination were not performed routinely for staging.

All slides were reviewed by 2 pathologists (A.B. and V.S.) for this study in a masked fashion. By selecting only patients who underwent enucleation at our center after 1989, we were able to include only those patients in whom the enucleated eye underwent a previously reported uniform procedure for pathologic examination.¹⁸ From 2009 onward, this technique was slightly modified to comply with the international consensus for pathologic processing of enucleated eyes with retinoblastoma.¹⁴ For this study, we classified patients according to 3 published definitions for choroidal invasion (**Table 2**). For this article, to avoid confusion with the terms, we use only the terms *massive* and *focal choroidal invasion* for all classifications and cases (**Figure**). The North American definition will be used as a standard for description and comparison with other classifications.

Children with isolated choroidal invasion were not scheduled to receive any adjuvant therapy after enucleation in any protocol. However, from 1995 onward, chemoreduction with carboplatin and vincristine sulfate with or without etoposide was offered to patients with bilateral disease in whom eye preserva-

Table 2. Probability of Event-Free Survival and Overall Survival According to the Different Classifications Used for Grading Choroidal Invasion and Adjuvant Therapy

Definition	No. of Patients	pEFS, %	pOS, %
IRSS-TNM			
Focal invasion (<3 mm of invasion)	132	99.2	99.2
Massive invasion (>3 mm of invasion)	35	94.2	98.7
P value		.04	.29
IRSS-French			
Focal invasion (less than whole-width invasion)	140	99.2	99.2
Massive invasion (whole-width invasion)	27	92.5	96.2
P value		.01	.10
HPG			
Partial invasion (less than half of the thickness of the choroid and a single tumor cluster)	92	98.9	98.9
Full invasion (more than half of the thickness invasion and/or more than 1 tumor cluster)	75	97.3	98.6
P value		.40	.80

Abbreviations: HPG, Hospital de Pediatría Juan P Garrahan; IRSS, International Retinoblastoma Staging System; pEFS, event-free survival probability; pOS, probability of overall survival.

tion was possible.¹⁹ Therefore, a cohort of patients actually received postoperative chemotherapy when one eye was enucleated and showed isolated choroidal invasion and the fellow eye underwent chemoreduction for conservative therapy. For the purpose of this analysis, this technique was considered adjuvant chemotherapy. In other bilateral or selected unilateral cases, some eyes were enucleated after failure of chemoreduction and showed isolated choroidal invasion on pathologic examination. In these cases, no adjuvant chemotherapy was used, and they are considered as such in the analysis.

Contingency tables were constructed, χ^2 or Fisher exact tests were used for categorical variables, and the Mann-Whitney test was used for continuous variables. Extraocular relapse (including orbital and metastatic relapse) was defined as the main event, event-free survival curves were calculated according to Kaplan-Meier, and survival status was updated to June 2011. Curve comparison was performed with the log-rank test. Because of the low number of events, no multivariate analysis was attempted.

RESULTS

Four hundred ninety-five patients with retinoblastoma eligible for our protocols were evaluated. Of these, 171 (34.5%) had isolated choroidal invasion according to our inclusion criteria. Two patients were excluded after pathologic review because microscopic scleral invasion was evident, and 2 were excluded because choroidal invasion was considered artifactual. All have survived free of disease. Therefore, 167 patients were evaluable for the study.

Median age at diagnosis was 17 months (range, 1-165 months), and the male to female ratio was 0.94. Median

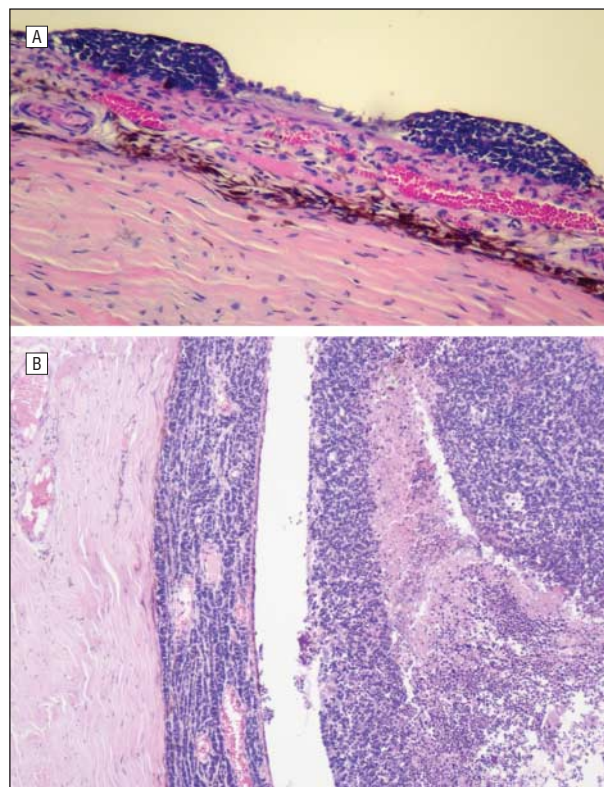


Figure. Choroidal invasion. A, Focal choroidal invasion including 2 tumor clusters measuring less than 3 mm. B, Massive choroidal invasion invading the whole thickness of the choroid.

follow-up was 44 months (range, 12-224 months). One hundred nine patients (65.3%) had unilateral retinoblastoma and 58 (34.7%) had bilateral retinoblastoma.

One hundred thirty-six children in our cohort did not receive any adjuvant chemotherapy (**Table 3**). However, 28 of them received preenucleation chemotherapy for conservative therapy. Twenty-three patients received postoperative chemotherapy with a median of 4 cycles (range, 1-8) of carboplatin and vincristine with (n=12) or without (n=11) etoposide for conservative therapy of the fellow eye as per a previously published schedule.¹⁹

Three children who underwent bilateral enucleation had choroidal invasion in both eyes. All of them had focal choroidal invasion, and all have survived free of disease.

According to the North American consensus definition, there were 132 children (79.0%) with focal choroidal invasion and 35 (21.0%) with massive invasion. Median extent of invasion was 0.55 mm (range, 0.02-2.5 mm) for those with focal involvement and 5 mm (range, 3-23.2 mm) for those with massive involvement ($P<.001$).

EVENTS

The 5-year event-free survival probability (pEFs) for the entire population was 98.1% (95% CI, 96.9%-1.0%), and the 5-year overall survival probability was 98.7% (95% CI, 97.8%-1.0%). Three patients (all unilateral, not receiving adjuvant therapy) experienced an extraocular relapse. These patients included 1 with massive invasion

Table 3. Patient Description and Outcomes According to the Use of Chemotherapy^a

Variable	Enucleation and No Chemotherapy (n = 113)	Initial Enucleation and Chemoreduction for the Fellow Eye (n = 28)	Enucleation After Failure of Chemoreduction and No Postoperative Chemotherapy (n = 23)
Focal choroidal invasion, No. (%)	86 (77.1)	24 (85.7)	19 (82.6)
Massive choroidal invasion, No. (%)	27 (23.9)	4 (14.3)	4 (17.4)
Concomitant prelaminar invasion, No. (%)	40 (35.3)	10 (35.7)	10 (43.4)
Concomitant anterior segment invasion, No. (%)	15 (13.2)	2 (7.1)	2 (8.6)
pEFS, %	97.2	100	100
pOS, %	98.2	100	100

Abbreviations: pEFS, event-free survival probability; pOS, probability of overall survival.

^aThree children who had choroidal invasion in both enucleated eyes were excluded because they received preoperative and postoperative chemotherapy.

who had an orbital relapse and was successfully treated with chemotherapy and radiotherapy and has survived free of disease for 21 years. Another patient with focal involvement had an orbital and bone marrow relapse and died despite treatment with conventional chemotherapy. The remaining patient with massive involvement had a combined orbital and central nervous system relapse and died of extraocular retinoblastoma despite therapy with high-dose chemotherapy and autologous stem cell rescue. Therefore, the 5-year event-free survival probability for children with focal choroidal invasion was 99.2% (95% CI, 98.6%-1.0%) vs 94.2% (95% CI, 89.7%-1.0%) for children with massive invasion ($P=.04$). However, this significant difference was lost when the 5-year overall survival probability was analyzed (99.2% [95% CI, 98.6%-1.0%] vs 98.7% [95% CI, 96.9%-1.0%]; $P=.29$).

Two children with bilateral retinoblastoma had secondary malignant tumors (limb osteogenic sarcoma in 1 patient and spinal ependymoma in 1 patient). Both survived after treatment (6 and 3 years from the diagnosis of the secondary malignant tumor, respectively).

EFFECT OF OTHER CONCOMITANT PATHOLOGIC RISK FACTORS

There were 62 children (45.6%) (14 with massive choroidal invasion) with concomitant prelaminar optic nerve invasion, and 2 of them had an extraocular relapse (both with massive choroidal involvement). No child with prelaminar optic nerve and focal choroidal invasion ($n=48$) had an extraocular relapse. The pEFS of children with associated prelaminar invasion was not significantly inferior to those without this feature (96.7% vs 99.0%, $P=.20$). The pEFS of children with massive choroidal invasion and prelaminar invasion was 85.7% com-

pared with 100% of those with massive choroidal invasion alone ($P=.07$).

Concomitant invasion of the anterior segment ($n=21$) was significantly more common in children with massive invasion (8 of 35 compared with 13 of 132 with focal invasion) ($P=.04$). Only one of the relapsing children had concomitant anterior segment invasion and massive choroidal invasion, whereas the rest remain disease free. The pEFS of children with associated anterior segment invasion was not significantly inferior to those without this feature (95.2% vs 98.6%, $P=.20$).

EFFECT OF ADJUVANT CHEMOTHERAPY

No statistically significant differences were found in pEFS among the groups with no chemotherapy, preoperative chemotherapy only, and adjuvant therapy (Table 3). However, no child receiving adjuvant therapy had an event, but the proportion of children with massive invasion was lower in the chemotherapy groups, and the median extension of choroidal invasion was marginally lower than that of children who did not receive adjuvant chemotherapy (0.6 vs 1.2 mm, $P=.10$).

COMPLICATIONS OF CHEMOTHERAPY

At least an episode of fever and severe neutropenia necessitating hospital admission occurred in 16 of 54 children (29.6%) who received chemotherapy before or after enucleation. Seven patients had systemic infections, including 1 admission to the pediatric intensive care unit because of gram-negative sepsis, but there were no chemotherapy-related deaths. Two patients needed transfusion support, and 1 patient had an episode of thrombotic microangiopathy attributed to carboplatin.²⁰

EVALUATION OF THE DIFFERENT DEFINITIONS FOR GRADING CHOROIDAL INVASION

Minor differences were found between the number of children in each category according to the North American and French definitions (Table 2). The definition previously used by our group tended to overestimate the number of children with massive invasion. The classification proposed by the French group was the one that identified more significantly the children with higher risk of relapse, but none was clearly superior to the rest in predicting survival.

COMMENT

This series is, to our knowledge, the first report on a large cohort of children with isolated choroidal invasion, mostly treated without adjuvant therapy, undergoing a detailed pathologic review to classify them according to the current consensus definitions reporting its long-term outcome. The relapse rate of our population is lower than previously reported. It was 1.8% in our population and 2.2% if only children who did not receive adjuvant therapy are considered, which is lower than a previously re-

ported series with comparable patients that reported up to 8.1% with an extraocular relapse.⁵

Our data confirmed that children with massive invasion have a significantly higher chance of having an extraocular relapse. The statistical significance of this finding depended on the classification used and whether only children treated with enucleation were included in the analysis. However, this significance was lost when survival was considered because some children can attain a second complete remission after an extraocular relapse. However, this population with a higher risk of relapse could only be accurately identified using the current consensus definitions for the degree of invasion. Nevertheless, a fatal systemic relapse occurred in a child with focal invasion as well. According to our data, the French definition might be able to predict with higher precision the occurrence of extraocular relapse, but it is still lower than 8%. Other authors, as well as our own previous definition, also include those children with multiple tumor foci in the choroid in the massive invasion subgroup.^{3,4} However, this is sometimes difficult to assess in a reliable fashion because eyes are examined microscopically in 2 dimensions and extensive invasion may appear as multifocal in different cut sections, especially when extensive sampling, including the calottes, is evaluated. However, because it also failed to include all patients in the high-risk group who relapsed, our previous classification overestimated the risk of lower-risk children, we are not using it anymore.

Therefore, because assigning the risk of extraocular relapse based only on the extent of choroidal invasion may not reliably identify all children at high risk, the invasion of other concomitant structures of the eye has been proposed as a way of identifying these children more accurately. Thus, other concomitant pathologic risk factors that are usually considered to be of lesser risk of relapse have also been proposed as potentially adding a higher risk for these patients. Some groups, including the recently updated TNM staging system,²¹ consider concomitant prelaminar optic nerve invasion as a specific subgroup, implying a putative higher risk for extraocular relapse in patients with focal choroidal invasion. Our data did not show a significantly increased risk of relapse from the association between prelaminar optic nerve involvement and focal choroidal invasion. However, the risk of extraocular relapse was marginally higher when this feature combines with massive choroidal invasion. Invasion to other structures of the eye, such as the anterior chamber or the anterior uvea, as seen when the ciliary body or the iris is involved has also been proposed as an indicator of a higher risk of relapse. Again, no significant difference was seen in our series, but invasion to the anterior segment was associated significantly with massive invasion. It was not possible to find any other risk factor in children with focal invasion because of their low relapse risk.

Therefore, the identification of a population that would unequivocally benefit from adjuvant therapy is difficult. With such a low relapse rate, a randomized study is not realistic to determine the beneficial effect of adjuvant therapy. Thus, the decision of giving adjuvant therapy to children with isolated choroidal invasion will always expose a substantial number of patients to unnecessary che-

motherapy to potentially prevent an extraocular relapse in a few. Until recently, the occurrence of extraocular relapse was considered a uniformly fatal event. However, with the use of high-dose chemotherapy and autologous stem cell rescue, up to 70% of the children with systemic metastasis and fewer of those with central nervous system relapse (2 of 4 in our South American experience) may be cured, even in middle-income countries, such as Argentina.²² Thus, withholding adjuvant therapy for all children with isolated choroidal invasion and treating aggressively those who relapse would be a reasonable alternative if high-dose chemotherapy and autologous stem cell rescue are available. This strategy for reducing the total burden of therapy without a reduction in survival is a standard practice in other pediatric malignant tumors, such as testicular yolk sac tumors.²³ It should be considered that large units in developing countries such as ours would have the higher burden of treating these patients with pathologic risk factors who are more common in that setting.¹⁰ It might be argued that giving adjuvant therapy would cure 100% of the patients instead of the 98% obtained in our series, which would justify the adjuvant treatment of children who do not need it to save the 2% of high-risk children. However, other factors associated with the use of chemotherapy in developing countries should be considered, such as the toxic mortality rates of active chemotherapy regimens, which were reported in many series, even with low-intensity regimens,²⁴ and the potential occurrence of secondary leukemias that affected 1% of our patients with retinoblastoma who received chemotherapy (data not shown). When all these issues are considered, the decision to give adjuvant therapy to children with isolated choroidal invasion becomes more difficult. Therefore, on the basis of our data, we can conclude that survival is not jeopardized by the decision to not give adjuvant chemotherapy to children with isolated choroidal invasion provided that 2 important conditions are available: reliable eye pathologic data and availability of effective second-line therapy. However, the situation in other developing countries with limited access to intensive therapy for relapse may shift this balance toward the use of adjuvant therapy. Our findings highlight the critical role of an expert pathologic examination of the enucleated eye to tailor adjuvant therapy to patients with massive invasion who might benefit from it, but only if fatal toxic effects associated with chemotherapy are kept to a minimum because the relapse rate is low. Other strategies to better estimate the risk of extraocular relapse of children with isolated choroidal invasion, such as the study of minimally disseminated disease, are currently being pursued by our group.

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