Outcome of Retinoblastoma Patients with High-risk Histopathological Features in a Tertiary Hospital

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ABSTRACT

Objectives: To describe the outcome of patients with bilateral or unilateral retinoblastoma with high-risk histopathological features managed at a tertiary hospital in the Philippines.

Methods: This was a descriptive, retrospective review of retinoblastoma cases with high-risk histopathological characteristics seen at a tertiary hospital from January 1999 to July 2012. Out of 239 patients, those with at least one of the following features were included in the study: positive cut optic nerve margin, postlaminar optic nerve involvement (PLONI), intra- or extrascleral involvement, choroidal invasion, and anterior segment involvement. We determined the number of patients who developed orbital recurrence and metastasis, otherwise known as events, within 1 year after enucleation or exenteration and compared the outcomes between those who received and did not receive adjuvant therapy.

Results: Of the 82 eyes of 79 patients with high-risk histopathologic features, 25.6% had orbital recurrence and 18.3% developed central nervous system, lymph node, or distant metastasis. None with isolated choroidal involvement (n=24) or combined choroidal and anterior segment involvement (n=4) developed recurrence or metastasis. Patients with isolated anterior segment (n=1) and PLONI with negative margin involvement (n=1) remained event-free with chemotherapy. The following developed orbital recurrences: 2 of 9 patients with combined choroid and scleral involvement, and 1 of 8 patients with PLONI negative margin and choroidal involvement. These patients did not receive immediate postoperative chemotherapy. Two out of 4 patients with isolated PLONI with positive margin of resection developed metastasis despite adjuvant therapy. Of 12 patients with combined choroid, scleral, or anterior segment and PLONI with positive margin involvement, only 3 of the 7 patients who received full chemotherapy remained event-free, while the rest developed orbital recurrence or metastasis (9 of 12). Of 17 patients with extrascleral involvement and varying degrees of intraocular involvement and optic nerve margin involvement, only 3 of the 9 who received full chemotherapy remained event-free, including two who received an intensive chemotherapy course.

Conclusion: Isolated choroidal and combined choroid and anterior segment involvement had no recurrences or metastasis either with or without adjuvant therapy. Patients with combined choroid and scleral involvement and those with PLONI, negative margin with choroidal involvement had better outcomes with adjuvant therapy than

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without. Patients with the following features developed events despite adjuvant therapy: positive optic nerve margin combined with any ocular tissue involvement, and extrascleral involvement combined with any other feature. We recommend giving a timely and complete chemotherapy regimen to prevent recurrence or metastasis in combined choroid and scleral involvement, and PLONI negative margin with choroidal involvement. We suggest intensive chemotherapy for patients with positive margin involvement or extrascleral involvement. Further studies are recommended to establish the need for chemotherapy in isolated PLONI.

Keywords: Retinoblastoma, Outcomes, High-risk, Histopathology, Extraocular.

Retinoblastoma has good prognosis with early detection and timely intervention. Overall survival from this disease is estimated at 90% in developed countries.[1] In developing countries, the survival rate is lower due to advanced stage at diagnosis and delayed treatment.[2] Mortality is primarily due to metastasis, which occurs in less than 10% of patients.[1] When metastasis or recurrence occurs, it usually manifests within 1 year after surgery.[3] In a retrospective study of 93 cases seen at the Philippine General Hospital from 1985 to 1990, orbital recurrence rate was 14 percent and the average onset of recurrence was at 19 months.[4]

Over the years, it has been shown that there are certain histopathologic features that increase the risk of orbital recurrence and metastasis. These include postlaminar optic nerve invasion (PLONI), invasion of cut optic nerve margin, choroidal, scleral, and anterior segment involvement.[5] The identification of these factors allowed for a more discriminate use of adjuvant therapy. Children without these features may be spared from unnecessary adjuvant therapy and its potential complications, such as myelosuppression and sepsis for chemotherapy,[6] severe orbital contracture for radiotherapy, and the possibility of secondary malignancies from both chemo- and radiotherapy.[7,8]

Universal guidelines for the use of chemo- or radiotherapy in high-risk retinoblastoma have yet to be established. The studies to date have sound, athough occasionally conflicting, recommendations. Authors unanimously agreed that PLONI with positive optic nerve margin involvement and those with scleral involvement must be treated with chemotherapy.[1,3,5,8,10] Choroidal involvement and PLONI with negative optic nerve margin were more controversial. Isolated choroidal involvement of any degree was considered by Chantada and Dunkel and Uusitalo to be low-risk and they, therefore, did not advocate chemoprophylaxis for these patients.[5,10] Khelfaoui and Honavar recommended giving chemotherapy in massive choroidal invasion,[1,8] and Shields advocated prophylactic orbital radiotherapy and/or systemic chemotherapy when choroidal involvement was associated with any degree of optic nerve invasion.[9] Chantada and Dunkel found that isolated postlaminar optic nerve invasion (PLONI) with a negative margin was not associated with a high risk of relapse and metastasis.[5] Chantada and Casco concluded that postlaminar optic nerve invasion (PLONI) with negative margin was a significant risk factor only when it was associated with choroidal or scleral invasion.[11] Khelfaoui, Uusitalo, and Honavar recommended giving adjuvant therapy to patients with postlaminar optic nerve involvement even with negative margin of involvement.[1,8,10]

In our institution, we are guided by the recommendations of foreign literature in deciding which patients should receive adjuvant therapy. In this descriptive retrospective study, we determined the outcomes of patients with high-risk ocular features seen in our institution. More specifically, we determined how many of our patients developed recurrence and metastasis within 1 year after surgery among those who received and did not receive adjuvant therapy. This allowed us to review our local experience with retinoblastoma, compared it with international studies, and eventually came up with our own recommendations in the appropriate use of adjuvant therapy for retinoblastoma with high-risk histopathologic features.

METHODOLOGY

A. Study design

We did a descriptive, retrospective review of charts and histopathological reports of retinoblastoma patients from January 1, 1999 to July 31, 2012.

B. Inclusion criteria

1. Retinoblastoma patients with unilateral or bilateral eye involvement, with the following histopathologic characteristics: postlaminar optic nerve involvement (PLONI), optic nerve margin involvement, scleral invasion, choroidal

invasion, or anterior segment involvement;
2. Patients with at least 12 months follow-up if there were no signs of orbital recurrence or metastasis, or less than 12 months if such recurrence or metastasis develops.

C. Exclusion criteria

1. Patients with signs of distant or regional metastasis on initial presentation;
2. Retinoblastoma patients without high-risk histopathological features;
3. Retinoblastoma patients who have high-risk features but have less than 12 months event-free follow-up.

D. Data Collection

Retinoblastoma case charts from the Ocular Oncology Clinic of the University of the Philippines-Philippine General Hospital (UP-PGH) Department of Ophthalmology and Visual Sciences from January 1, 1999 to July 31, 2012 were reviewed. In instances where there were incomplete histopathologic reports, review of slides were performed by ocular pathologists (RED and RV) at the Institute of Ophthalmology. Charts were retrieved from the Department of Pediatrics, Section of Hematology-Oncology, to collect information on chemotherapy regimens and outcomes. Patients received the standard chemotherapy regimen consisting of vincristine, etoposide, and carboplatin for 6 to 8 cycles unless specified otherwise. The Argentina Protocol, which included cyclophosphamide and doxorubicin in addition to vincristine, etoposide, and carboplatin, was occasionally given for orbital recurrences and systemic or intracranial metastasis.

The selected population was grouped according to the high-risk feature/s they possessed (Tables 1, 2, 3). The groups were further subdivided into whether they received no adjuvant therapy prior to the development of orbital recurrence or metastasis, full chemotherapy, or incomplete chemotherapy. Adjuvant therapy referred to either chemotherapy or radiotherapy. Full chemotherapy consisted of 6 or more cycles, while incomplete chemotherapy meant less than 6 cycles of chemotherapy. If radiotherapy was given, it would be indicated in the text. The number of patients who developed orbital recurrence or metastasis, otherwise known as events, were tallied for each subgroup. The percentage of patients who remained event-free at the end of 12 months was calculated for each high-risk feature.

Table 1. Outcomes of patients with single high-risk histopathological feature.

High-risk feature	Patients with Events*			% Event-free after 1 year
	No adjuvant therapy	Full chemotherapy[&]	Incomplete chemo[$]	
Isolated choroid	0 (n=9)	0 (n=9)	0 (n=6)	100%
Isolated AC[#]	(n=0)	(n=0)	0 (n=1)	100%
Isolated PLONI negative margin	(n=0)	0 (n=1)	(n=0)	100%

* Orbital recurrence or metastasis
[&] Full chemotherapy – more than 6 cycles of chemotherapy
[$] Incomplete chemotherapy – less than 6 cycles of chemotherapy
[#] AC-anterior chamber or segment involvement

Table 2. Outcomes of patients with multiple high-risk histopathological features limited to intraocular structures.

High-risk feature	Patients with Events*			% Event-free after 1 year
	No adjuvant therapy	Full chemotherapy[&]	Incomplete chemo[$]	
Choroid + AC[#]	0 (n=1)	0 (n=3)	(n=0)	100%
Choroid + sclera	2 (n=4)	0 (n=5)	(n=0)	77.7%
Choroid + sclera + AC	(n=0)	1 (n=2)	(n=0)	50%

* Orbital recurrence or metastasis
[&] Full chemotherapy – more than 6 cycles of chemotherapy
[$] Incomplete chemotherapy – less than 6 cycles of chemotherapy
[#] AC-anterior chamber or segment involvement

Table 3. Outcomes of patients with multiple high-risk histopathological features involving extraocular structures.

High-risk feature	Patients with Events*			% Event-free after 1 year
	No adjuvant therapy	Full chemotherapy[&]	Incomplete chemo[$]	
PLONI[**] negative margin + choroid	1 (n=1)	0 (n=5)	0 (n=2)	87.5%
PLONI with positive margin	(n=0)	2 (n=4)	(n=0)	50%
PLONI positive margin + choroid +/-AC[#]	(n=0)	1 (n=3)	2 (n=2)	40%
PLONI positive margin + choroid + sclera +/- AC	1 (n=1)	3 (n=4)	2 (n=2)	14.3%
Extrascleral +choroid +/- AC	1 (n=1)	1 (n=2)	2 (n=2)	20%
Extrascleral + PLONI with negative margin +choroid +/-AC	1 (n=1)	1 (n=2)	(n=0)	33.3%
Extrascleral + PLONI with positive margin + choroid +/- AC	3 (n=3)	4 (n=5)	1(n=1)	11.1%

* Orbital recurrence or metastasis
[&] Full chemotherapy – more than 6 cycles of chemotherapy
[$] Incomplete chemotherapy – less than 6 cycles of chemotherapy
[#] AC-anterior chamber or segment involvement
** PLONI - postlaminar optic nerve invasion

RESULTS

A. *Patient characteristics*

We reviewed 239 retinoblastoma patient files seen at our institution between January 1, 1999 and July 31, 2012. Of the 79 patients who met our selection criteria, 55 had unilateral retinoblastoma and 24 had bilateral involvement. Only 3 of 24 patients had both eyes included in the study. Of the remaining 21 patients with bilateral involvement, 2 patients had incomplete histopathological reports for the other eye, 15 underwent successful globe-sparing treatment for the other eye, and 4 had no high-risk histopathologic features in the other eye. We evaluated a total of 82 eyes in 79 patients for our study. Follow-up ranged between 3 to 686 weeks (13.2 years) with a mean follow-up of 182 weeks (3.5 years).

B. *Single high-risk feature*

There were 24 eyes with isolated choroidal invasion. Nine received full courses of chemotherapy, 6 of which were for bilateral ocular involvement and the rest for unilateral involvement. Six received less than 6 cycles of chemotherapy, 2 of which were for bilateral involvement, and the rest for unilateral involvement. Nine were not prescribed chemotherapy. None of these patients developed orbital recurrence or metastasis within 1 year of surgery.

There was only 1 patient with isolated anterior chamber involvement who received 1 cycle of the standard chemotherapy regimen. This patient did not develop recurrence or metastasis.

We found 1 patient with isolated post-laminar optic nerve involvement with negative cut optic nerve margin. This patient was given a complete cycle of chemotherapy and was event-free at 1 year post-enucleation.

C. *Multiple high-risk histopathological features limited to intraocular structures (choroid, sclera, or anterior segment)*

There were 4 eyes with combined choroid and anterior segment involvement. Three received a full course of chemotherapy as chemoreduction for bilateral involvement and 1 was not prescribed chemotherapy after bilateral enucleation. These patients had a 100% event-free rate at 1 year post-enucleation.

Nine patients had combined choroid and scleral involvement. Five patients received a full course of chemotherapy and 4 refused chemotherapy after enucleation. Two of the four patients who did not receive chemotherapy immediately postoperatively developed orbital recurrence and maxillary metastasis. Despite attempts to rescue these patients with chemotherapy, one patient died from metastasis after 7 cycles, while the other was lost to follow-up. The event-free rate for patients with combined choroid and scleral involvement in this study was 77.7% at 1 year postenucleation.

There were two patients with combined choroid, scleral, and anterior segment involvement who both received full courses of chemotherapy. One of the two developed orbital recurrence at 14 months after surgery. This patient received 6 cycles of chemoreduction preoperatively. When recurrence was noted, the patient was advised to get chemotherapy prior to exenteration but the patient became lost to follow-up.

D. *Multiple high-risk histopathological features involving extraocular structures (PLONI, optic nerve margin involvement, extrascleral involvement)*

Eight patients had combined choroid and postlaminar optic nerve invasion with negative margin involvement. One patient refused chemotherapy, 5 received full courses, and 2 patients received incomplete courses. Only the patient who refused chemotherapy developed orbital recurrence. One of the 2 who received less than 6 cycles of chemotherapy also received cobalt therapy. The event-free rate for these patients at 1 year postenucleation was 87.5%.

Four patients had combined postlaminar optic nerve involvement (PLONI) with positive cut optic nerve margin involvement, all of whom received complete courses of chemotherapy. Two of the four died from metastasis. One of the two who survived also received cobalt therapy aside from chemotherapy. These patients have a 50% event-free rate at 1 year after surgery.

There were 5 patients with combined PLONI, positive cut optic nerve margin, and choroid with or without anterior segment involvement. One of 3 patients who received complete chemotherapy and 2 of 2 patients who received incomplete cycles developed orbital recurrences. The event-free rate for this group was 40% at the end of 1 year.

Seven patients had combined PLONI, positive cut optic nerve margin, choroid, and scleral involvement with or without anterior segment involvement. One out of one patient who did not receive chemotherapy, 3 out of 4 patients who received complete courses, and 2 out of 2 patients who received incomplete courses developed orbital recurrences. The event-free rate for this group was 14.3%.

Five patients had combined extrascleral and choroid with or without anterior segment involvement. One out of one patient who did not receive chemotherapy, 1 of 2 patients who received a complete cycle, and 2 of 2 patients with incomplete chemotherapy developed orbital recurrences and/or metastases. The only patient who did not develop an event was given the Argentina Protocol, which was a more intensive regimen. The event-free rate for this group was 20% at 1 year after surgery.

Three patients in our study had combined extrascleral involvement, PLONI with negative optic nerve margin, and choroid with or without anterior segment involvement. One of one patient who did not receive chemotherapy and 1 of 2 patients who received complete cycles developed orbital recurrences and metastases. Both of these patients died from metastasis. The event-free rate for this group was 33.3%. The only patient who did not develop orbital recurrence or metastasis received the Argentina Protocol.

There were 9 patients with combined extrascleral, PLONI, positive cut optic nerve margin, and choroid with or without anterior segment involvement. Three of these patients refused chemotherapy, 1 received 1 cycle before developing orbital recurrence, and 5 received full courses, of whom 1 also received radiotherapy. Of these patients, only 1 of the 5 patients who received full courses remained event-free at 1 year. The patient who received radiotherapy developed recurrence and metastasis and eventually died. The event-free rate for this group was 11.1%.

E. *Outcome for the entire group with high-risk histopathologic features*

We calculated the recurrence rate and metastasis rate at 25.6% and 18.3% respectively, for patients with high-risk histopathologic features included in our study. The average onset of orbital recurrence or metastasis was at 4 months, with a range from 3 weeks to 14 months. The over-all event-free rate of our patients at 1 year postenucleation was 65.1%.

DISCUSSION

Our results showed that retinoblastoma with isolated choroidal involvement did not have an increased incidence of recurrence or metastasis without adjuvant therapy compared to those treated with adjuvant therapy. Patients with combined choroid and scleral involvement and those wih PLONI, negative margin and choroidal involvement each had lower incidence of events with chemotherapy than without. Patients with the following features developed events despite adjuvant therapy: PLONI with positive optic nerve margin involvement combined with any ocular tissue involvement, and extrascleral involvement combined with any other feature.

The event-free rates we obtained in our study reflected the aggressiveness of a certain histopathologic feature or the success or failure of adjuvant therapy. We cannot distinguish between the two because the nature of retinoblastoma prevented us from performing randomized controlled trials on this disease. The high event-free rate that we obtained for isolated choroidal involvement reflected the low incidence of recurrence even when chemotherapy was withheld, which was consistent with the findings of Chantada and Dunkel and Uusitalo.[5,10] We did not make a distinction between minimal or massive choroidal invasion as in other studies[1,8] because of our limited sample size and because of discrepancies in the reporting of these findings. Chantada and Dunkel and Uusitalo believed that labelling choroidal invasion as minimal or massive could be subjective and was not uniformly used; hence, they avoided making the distinction.

Our findings suggested that patients with combined choroid and scleral involvement and those with PLONI with choroidal involvement would benefit from chemotherapy, which was similar to the findings of other authors.[1,5,8] These patients had no recurrences with the standard chemotherapy regimen given at our institution. The low event-free rates we obtained for PLONI with positive optic nerve margin and extrascleral involvement were as expected, but we had higher incidences of recurrences despite adjuvant therapy compared to other studies.[1,8] We found that most of the patients who did not develop events in this group received a more intensive chemotherapy

regimen, the Argentina protocol, than the others. We were unable to get enough subjects with combined choroid and anterior segment involvement, isolated PLONI with negative optic nerve margin and isolated anterior segment involvement, which prevented us from making any conclusions regarding these features. Some studies, despite their similarly small sample sizes, proposed that anterior segment involvement did not carry a high risk for recurrence or metastasis.[5,10] Isolated PLONI with negative margin was considered high-risk by most authors and should be given chemoprophylaxis.[1,8,10]

We had higher rates of recurrences and metastasis in patients with PLONI with positive cut optic nerve margin and those with extrascleral involvement than in other studies. The presence of these features indicated that the tumor had been left behind; hence, early chemotherapy was essential in these patients. Recurrences and metastasis despite complete adjuvant therapy might be due to delayed and irregular administration of the chemotherapy cycles, or it might reflect the inadequacy of the standard chemotherapy regimen used in our institution for these factors. Unfortunately, we could not distinguish between the two because of non-uniform reporting of these factors in our charts.

The metastasis rate was higher in our study than that reported in the literature[1] because the population of our study was selectively high-risk. Socioeconomic factors also affected our patients' compliance with chemotherapy, contributing to the higher metastasis and recurrence rates seen. In our study, the average time of onset of metastasis was at 4 months after enucleation. We had 1 patient who developed metastasis at 14 months after enucleation. In one local study, the maximum interval between enucleation and appearance of signs of recurrence was 4 years.[4] Although most recurrences and metastasis appear within 1 year after surgery, patients should be followed-up for at least 2 years or more.

The main limitation of this study was the small sample size, which was also an issue in other similar studies. In our study, the small sample size was due to the large number of patients who were lost to follow-up after enucleation, and to those that dropped out after completing chemotherapy. Because of this, we were unable to get event-free rates at more than 1 year after surgery, and we were unable to estimate the overall survival rate of our high-risk patients. The frequent problem of small sample sizes may be overcome by multicenter collaborations.

We recommend giving a timely and complete chemotherapy regimen to prevent recurrence or metastasis in combined choroid and scleral involvement, and PLONI negative margin with choroidal involvement. We suggest intensive chemotherapy for patients with positive optic nerve margin involvement and extrascleral involvement. We also suggest that chemotherapy be deferred for patients with isolated choroidal involvement provided that the patient can be closely monitored after surgery. All patients who underwent enucleation must be followed-up for at least 2 years after surgery to monitor for recurrence or metastasis. Further studies are encouraged to determine the importance of adjuvant therapy for PLONI with negative margin.

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