LETTER TO THE JOURNAL

High Risk Retinoblastoma: Prevalence and Success of Treatment in Developing Countries

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Retinoblastoma is the most common intraocular malignancy of infancy and early childhood. Its incidence is around 1 in 20,000 live births.\textsuperscript{1} Reported discrepancies between developing and developed countries include access to health care, lack of well-established tertiary care centers, and disease awareness among the population. All those factors contribute to the increased risk of disease dissemination.\textsuperscript{2–6}

Upfront enucleation is the treatment of choice for children with advanced intraocular retinoblastoma. Patients planned for enucleation do not receive chemotherapy since it’s been reported to potentially under-stage the disease.\textsuperscript{7,8}

Retinoblastoma with high risk histopathologic features poses a challenge since there is no consensus on how high risk feature cases should be treated as well as the discrepancies in definition of those features. The goal with adjuvant chemotherapy is to prevent extra-ocular metastasis.\textsuperscript{9,10}

Our aim in this study was to identify the eyes that had undergone enucleation with no prior administration of chemotherapy, to measure the prevalence of histopathologic high risk features and to assess the survival of those patients seeking evidence behind the administration of adjuvant chemotherapy to each risk group.

Children’s Cancer Hospital – Egypt (CCHE) retinoblastoma study team started a standard treatment protocol for high risk features retinoblastoma in January 2011. Scientific and ethical committees have approved the study. Bilateral cases and patients who received any chemotherapy prior to surgery were excluded.

All patients had baseline radiological, clinical and ocular examination and eyes were classified according to the International Classification of Retinoblastoma (ICRB).\textsuperscript{11} Unilateral cases staged as group C, D or E and above the age of 2 years were indicated for enucleation. Enucleated eyes were processed for identification of high risk features.\textsuperscript{12} Eyes that were found to have massive choroidal invasion or post laminar optic nerve invasion or any degree of choroidal invasion with any degree of optic nerve invasion in their pathology reports received a high risk feature regimen. Drugs used in the regimen were Vincristine (0.05 mg/kg, or 1.5 mg/m\textsuperscript{2}), carboplatin (18.6 mg/kg or 560 mg/m\textsuperscript{2}) on day 1 and etoposide (56 mg/kg or 150 mg/m\textsuperscript{2}) on days 1 and 2 for a total of six cycles (the cycle is 21 days). Dose was based on surface area for children older than 3 years old. As for eyes with scleral invasion, those patients were screened for metastasis and received the COG ARET0321 protocol regimen. After our original analysis, we re-classified our patients data based on other publications\textsuperscript{10,13} to facilitate comparisons.

During the reporting period (after January 2011), 81 unilateral cases underwent primary enucleation and 33 (40.74\%) had High Risk features. Mean duration of symptoms was 12.47 weeks, SD ± 20.69 (median 4) (reported for 30 patients). There was no statistically significant difference (\(p\) value = 0.1296) between duration of symptoms (resembling delay of access to healthcare) (16.5 weeks) and gender.

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Moreover, there was no difference in lag time to enucleation between males and females.

Initial ICRB was C in one patient, D in 7 (21.2%) patients and E in 25 (75.76%) patients. Correlating the initial classification with the pathological findings didn’t show statistically significant correlations. Mean time to enucleation was 0.54 months (median = 0.49). Table 1 illustrates the choroid and optic nerve involvement.

All the patients completed six cycles of chemotherapy with no grade III or IV adverse events. Median follow up time was 14.47 months (Mean = 15.49, SD ± 9.74). Overall and event free-survival were 100% at the median follow-up time. None of the patients had died or relapsed before submitting this article. See online supplementary material.

Retinoblastoma shows international distinctions between developed and developing countries. Such differences include distribution of intra-ocular and extra-ocular disease. Egypt as a lower-middle income country has a lower potential for survival of retinoblastoma patients.4,14 It can be attributed to delay in diagnosis and enucleation refusal. 6,15 This leads to a majority of retinoblastoma cases being diagnosed at advanced stages. Advanced intra-ocular tumors have higher risk for recurrence and progression into extra-ocular disease.16,17

The decision to enucleate an eye is usually based on many parameters, one of which is the extent of the involvement of intraocular structures, tumor size and age of the child especially with the absence of genetic testing.18 Despite the definitive and destructive nature of enucleation there is an agreement on its importance for unilateral advanced disease in order not to jeopardize the survival for the sake of eye salvage.19 Some studies showed that delaying enucleation for the sake of initial chemotherapy in patients with advanced eyes can mask important pathological features and increase the risk of metastasis.7,8,20

It has been shown that certain histopathological factors could be associated with an increased risk of metastasis or local recurrence. And in that case, 97% of orbital recurrence occurs in the first 12 months in high risk patients.21 Where administration of adjuvant chemotherapy with or without radiotherapy acts as a prophylaxis against disease progression.20,22,23 Moreover, certain clinical features can assist in predicting the underlying pathological features.24 However, there are standing disparities in these risk definitions.5,13

Choroidal invasion represents a risk for metastasis due to facilitation of tumor invasion through emissary vessels, and although it’s considered a risk for metastasis, administering adjuvant chemotherapy for independent choroidal invasion is still a controversial issue.25

Finding out that about 40% of our unilateral patients have risk features alerts physicians in developing countries to the fact that almost half of their patients are liable to tumor dissemination.

Our team agreed on choosing Children’s Oncology Group criteria for high risk features because they fit with recent International Classification for Retinoblastoma (ICRB) and International Staging for Retinoblastoma.26 Moreover, choroidal and optic nerve invasion is considered to have reliable evidence for its relation with post-enucleation relapse.17,27–29 Furthermore, our observations showed that isolated minimal or pre-laminar invasion does not end with orbital relapse. A recent study devised a more a stratified method for grouping patients.10 Our patients were located in the low risk group of Aerts and colleagues’ study (including patients with concurrent minimal choroidal and pre-lamina invasion who didn’t take chemotherapy) and intermediate risk (for the rest of the patients).10 Results didn’t show outcome difference against ours and thus we postulate that chemotherapy is not indicated in the latter group due to the risk of over-treating large cohort of patients (n = 22, 66.6%).

Finally, our study found the addressed high risk features controllable via the chemotherapy regimen in use in developing countries. We have started another study for stage 1 extra-ocular retinoblastoma for assessing the success of more intensive chemotherapy for this group. As well as discovering the prevalence of such features in our patient population and treatment effect, this treatment protocol enhanced the pathology team’s capabilities for ocular examination.

TABLE 1. Extent of optic nerve invasion and choroid involvement.

| Extent of optic nerve invasion                          | Less than 3 mm | More than 3 mm | No choroid involvement | Total |
|--------------------------------------------------------|----------------|----------------|------------------------|-------|
| No invasion                                            | 0              | 1              | 0                      | 1     |
| Anterior to lamina cribrosa                            | 11             | 2              | 0                      | 13    |
| At lamina cribrosa                                     | 11             | 3              | 0                      | 14    |
| Posterior to lamina cribrosa but not to end of nerve    | 2              | 2              | 1                      | 5     |
| Total                                                  | 24             | 8              | 1                      | 33    |

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DECLARATION OF INTEREST

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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Supplementary Material Available Online
Supplementary Data