



Original Article

# Retinoblastoma: An institutional experience

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## Keywords:

Histopathology;  
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## ABSTRACT

**Background:** This article aims to describe histopathologic high risk tumor characteristics in our patient population of retinoblastoma. It is based on consensus criteria for definitions of choroidal and optic nerve invasion as outlined in The International Retinoblastoma Staging Working Group (IRSWG) 2009.

**Materials and Methods:** Fifty histopathologically diagnosed cases of retinoblastoma were archived from records of Pathology department during years 2004 to 2014. Re-evaluation of slides to identify choroidal and optic nerve invasion as per IRSWG along with Pathologic tumor staging was done. Data were entered into Microsoft excel sheets and results expressed in percentages. Department of Ophthalmology was consulted for recurrence of Retinoblastoma.

**Results:** Among fifty cases, Choroidal invasion was absent in 62% cases. Minimal invasion (<3mm) was seen in 18% cases, massive (>3mm) in 14% cases and extra ocular involvement in 6% cases. The optic nerve was free of tumor in more than three fourth of the cases (78%). Prelaminar and retro laminar involvement of optic nerve was observed in 6% and 10% cases respectively. Intraocular spread of tumor was observed in 6% of cases. The cut margin of optic nerve was involved in 42% while it was free of tumor in 58% of cases. Significant number of tumours were pathologically classified as pT1 (58%) followed by pT2a (22%). pT3a and pT4b were found in 6% each and pT3b and pT4a were found in 4% each. Recurrence was observed in two cases of pT3a and one of pT4b.

**Conclusion:** We conclude identifying low percentages of high risk characteristics in a retrospective histologic experience with Retinoblastoma. Recurrence observed in two tumours staged pT3a sheds light on prognostic significance of reporting massive choroidal invasion despite free cut margin. These observations call for routine practice of standardized histopathologic reporting and processing of enucleated eye samples at our tertiary care centre.

## INTRODUCTION

Retinoblastoma is the most common intraocular malignant childhood tumor.<sup>1</sup> Intracranial spread and systemic metastasis are the main causes for mortality in patients with retinoblastoma.<sup>2</sup> Reduction in the rate of systemic tumor

dissemination by identification of high-risk histopathology factors after enucleation followed by appropriate adjuvant chemotherapy help improve survival.<sup>3</sup> The current era of utilization of chemotherapy for retinoblastoma has prompted the need to standardize examination of enucleated eyes and evaluate prognostic factors.<sup>4</sup> Currently, there is controversy about the definitions for choroidal invasion and an inconsistency in the handling of eyes with Retinoblastoma. The International Retinoblastoma Staging Working Group (IRSWG) in 2009 proposed consensus

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criteria for definitions of choroidal and optic nerve invasion agreed upon as histopathologic high risk characteristics for Retinoblastoma.<sup>5</sup>

## MATERIALS AND METHODS

The study has been approved by the institutional research committee. Fifty (50) histopathologically diagnosed cases of retinoblastoma were retrospectively archived from records of Pathology department during years 2004 to 2014. Re-evaluation of slides to identify choroidal and optic nerve invasion along with Pathologic tumor staging was done as per the consensus of IRSWG. However the gross handling of enucleated specimens was not in tune with the proposed criteria owing to the retrospective nature of the study.

Pathologic staging was done as per AJCC 2010. Data were entered into Microsoft excel sheets 2007 and results expressed in percentages. Department of Ophthalmology: clinical recurrence of tumors and further correlated

## IRSWG PROPOSED CONSENSUS CRITERIA

### DEFINITIONS:

• **CHOROIDAL INVASION:** Massive choroidal invasion: a max “d” of invasive tumor focus of 3 mm/> that may reach the scleral tissue.

Focal choroidal invasion: tumor focus < 3 mm and not reaching the sclera.

**OPTIC NERVE INVASION:** Optic nerve invasion were categorized as Prelaminar, laminar, retrolaminar, or tumor at surgical margin.

## RESULTS

Maximum numbers of children 14 cases (28%) of Retinoblastoma (fig.1) were in the age group of 36 months. It was interesting to observe the occurrence of Retinoblastoma in high frequency 42 cases (84%) amongst children from India. The tumor was found to be present in posterior chamber only in most of the cases, 29 cases (58%), followed by posterior chamber and uveal tract in 13 cases (26%). Whole eyeball involvement was seen in 6 (12%) cases. Both chambers and uveal tract only were involved in one case (2%) each. Undifferentiated tumor histology was seen in more cases, 30 cases (60%) while differentiated tumor type was seen in 20 (40%) cases. In 32 (68%) cases histologic high risk factor such as choroid invasion was absent but was present in 32% of cases.(fig.2) Invasion of <3mm of choroid was 9 (18%) cases while >3mm choroid invasion accounted for 7 (14%) cases. Optic nerve was not involved in 39 (78%) cases. Parts of optic nerve involved in descending order of frequency were 4 (8%) retrolaminar (fig.3), 3 (6%) prelaminar and 1 (2%) laminar. In 3 (6%)

**Table 1: Comparison of Choroidal Invasion in various reported series.**

Source, year	Total Choroidal Invasion, No./Total Eyes (%)	Massive Choroidal Invasion, No./Total Eyes (%)
Shields et al, 1993	67/289 (23.1)	NA
Khelifaoui et al,1996	73/172 (42.0)	20/172 (11.6)
Biswas et al,2003	78/232 (33.6)	51/232 (22.0)
Gupta et al,2009	57/142 (40.1)	39 (27.5)
Orellana et al,2009	NA	45/109 (41.3)
Eagle et al,2009	49/297 (16.5)	NA
Wilson et al,2011	41/67 (61.5)	17/67 (25.7)
Kashyap et al,2012	289/609 (47.5)	150/609 (24.6)
Present study	19/50 (38)	10/50 (20)

**Table 2: Comparison of Optic Nerve Invasion in various reported series**

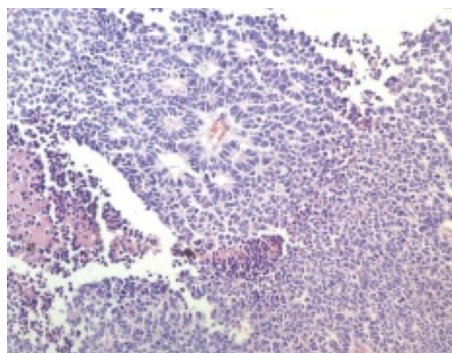
Study, year	Retrolaminar Optic Nerve, No./Total Eyes (%)	ResectedMargin, No./Total Eyes (%)
Shields et al,1994	17/289 (5.8)	2/289 (0.7)
Khelifaoui et al,1996	33/172 (20.0)	17/172 (10.0)
Magramm et al,1989	66/841 (28.0)	51/841 (21.0)
Gupta et al,2009	24/142 (16.9)	11/142 (7.7)
Orellana et al,2009	22/109 (20.2)	22/109 (20.2)
Eagle et al,2009	31/297 (10.4)	1/297 (0.34)
Wilson et al,2011	10/67 (14.9)	NA
Kashyap et al, 2012	98/609 (16.1)	45/609 (7.4)
Present study	2015 4/50 (8)	3/50 (6)

cases, extraocular involvement was also seen (fig.4). The cut margin of optic nerve was free in 29 (58%) cases while it was involved by the tumour in 21 (42%) cases.

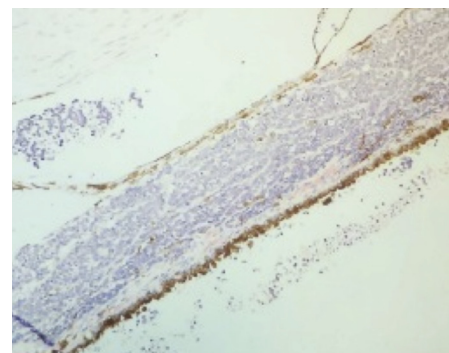
Significant numbers of tumours were pathologically classified as pT1 29 (58%) cases followed by pT2a 11 (22%) cases. pT3a and pT4b were found in 3 (6%) cases each and pT3b and pT4a were found in 2 (4%) cases each. Recurrence was observed in two cases of PT3a and one of pT4b (6%).

## DISCUSSION

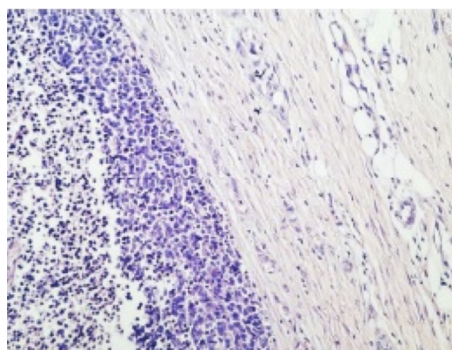
The incidence of retinoblastoma is constant worldwide at one case per 15,000–20,000 live births, which corresponds to about 9000 new cases every year.<sup>6</sup> The disorder has no validated geographic or population hotspots. The greatest disease burden is recorded in large populations that have high birth rates, such as in Asia and Africa.<sup>7</sup> Retinoblastoma is diagnosed relatively earlier in developed world while it is diagnosed later in developing countries, such as in Asia and Africa.<sup>7,8</sup> This is in concordant with our study where the



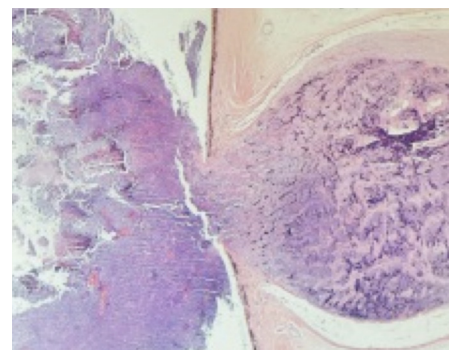
**Figure 1:** Photomicrograph showing formation of rosette in retinoblastoma (HE stain, X200)



**Figure 2:** Choroidal invasion by tumor cells (HE stain, X200)



**Figure 4:** Invasion by tumor cells into extraocular soft tissue (HE stain, X200)



**Figure 3:** Post-laminar invasion of optic nerve (HE stain, X20)

mean age at diagnosis was at a later age of 34.32 months (SD 21.2). Anterior chamber involvement by retinoblastoma is correlated with larger tumor size and is also considered as a risk factor by some authors. In our study anterior chamber was found to be involved in 14% cases which is comparable to the study done by some authors who reported it in 10% and 9% of enucleated eyes.<sup>9,10</sup> In the current study, most common site of involvement by tumor is posterior chamber (58%) followed by posterior chamber and uveal tract (26%), posterior chamber along with anterior chamber and uveal tract (12%) while there were single case each (2%) of isolated uveal tract only and both chambers without concomitant involvement of uveal tract. Poorly differentiated retinoblastomas have been reported to be associated with higher recurrence.<sup>9</sup> In our study most of the tumors were poorly differentiated (60%) while 40% were well differentiated. Similar occurrences were reported in other series as well.<sup>11,12</sup> On the other hand Filho et al found 95% of well-differentiated tumor in their series.<sup>13</sup>

There was a wide variation in the definition of risk criteria and in the criteria for giving adjuvant chemotherapy following enucleation. Definition of high-risk histological features and the criteria for use of adjuvant therapy is of utmost importance for the better prognosis of this potentially curable disease.<sup>14</sup>

This current era of utilization of chemoreduction and adjuvant chemotherapy for retinoblastoma mandate the

need to recognize risk factors and standardize criteria across institutions and countries. To address this problem, International Retinoblastoma Staging Working Group (IRSWG) has proposed consensus criteria.

Known risk factors for systemic metastasis include involvement of the choroid, orbital tissues, retrolaminar optic nerve and involvement of the optic nerve to the line of transection. The need to identify histopathologic risk factors (HRFs) for metastasis after enucleation and to provide appropriate adjuvant therapy has been emphasized.<sup>10</sup> In our study the histopathological re-evaluation of retinoblastoma as per the criteria of IRSWG revealed 20 % cases of massive choroidal invasion (including 6% extraocular extension) which is comparable to that in various series,<sup>9,10,15</sup> while Khelifaoui et al reported 11.6% and Orellana et al reported highest of all (41.3%).<sup>9</sup> (Table 1)

The published rates of recurrence due to optic nerve invasion shows a wide range: 7% to 56% for invasion of retrolaminar optic nerve and optic nerve to the transection line, 12% to 42% for choroidal involvement and 3% to 30% for scleral and extrascleral spread.<sup>10</sup> The IRSWG consensus criteria for optic nerve invasion include classification as prelaminar, laminar, retrolaminar and surgical cut margin.<sup>5</sup> We found that prelaminar invasion in 6%, laminar invasion in 2%, retrolaminar invasion in 8% and tumor at surgical cut margin in 6% cases. Retro laminar and surgical cut margin involvement by retinoblastoma has higher rate of recurrence

and are hence risk factors.<sup>16</sup> (Table 2).

Recurrence of malignancy is described as the reappearance of tumour cells or disease when it had apparently been eliminated. The first study examining the recurrence of retinoblastoma was done on patients enucleated between 1878 and 1929. It was published by Algernon B. Reese, and it gave a projected rate of orbital recurrence of 72%. In particular, this report addressed the importance of histopathological data and the surgeon's expertise. Arif M. et al reported an orbital recurrence rate as approximately 23% and proptosis and fungating mass were considered factors that can result in orbital recurrence.<sup>17</sup> In a large retrospective study by Kim et al. reviewing 1674 retinoblastoma patients who underwent enucleation between 1914 and 2006, seventy-one cases (4.2%) of orbital recurrence were identified.<sup>17</sup>

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Histopathologic features of advanced tumor stage govern the most crucial part of disease management. In our part of world due to lack of awareness, accessibility to health care facility, resources as well as lack of policy of government, usually patients seek medical help late and hence are diagnosed in advanced stage. In the current study, significant numbers were pathologically classified as pT1 (58%) followed by pT2a (22%). pT3a, pT3b, pT4a and pT4b were found in 6%, 4%, 6% and 4% respectively. 20% were found to be pT3a and higher. Recurrence was observed in three cases including two cases of massive choroidal invasion despite free cut margin.

## CONCLUSION

The IRSWG protocol helped identify massive choroidal invasion in 14%, extraocular extension in 6%, and retrolaminar involvement of optic nerve in 8% cases. Recurrence observed in two tumours staged pT3a sheds light on prognostic significance of reporting massive choroidal invasion despite free cut margin. These observations call for routine practice of standardized histopathologic reporting and processing of enucleated eye samples at our tertiary care centre.

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