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## Review Article

# Orbital retinoblastoma: Where do we go from here?

### ABSTRACT

Diagnosis of orbital retinoblastoma traditionally carries a dismal prognosis. Although its incidence is less in the developed countries, it continues to contribute to an epidemic of extraocular disease at diagnosis in the developing world. Orbital retinoblastoma encompasses a wide range of distinct clinical entities with varying tumor load. There are no standard treatment protocols as of now but the current preferred management is multimodal with a combination of initial high-dose chemotherapy, surgery, external beam radiotherapy and prolonged chemotherapy for 12 cycles. Though orbital retinoblastoma is a catastrophic event, rapid advances on many fronts, especially the genetic, makes the future appear brighter than what it is now. This review looks at all the new frontiers that are in store in the near as well as the distant future. Looking at the ever expanding horizons makes one believe of a definite hope that one day we will conquer this disease as we have conquered many others in the past.

**KEY WORDS:** Extraocular, future, orbit, RB1 gene, retinoblastoma

### INTRODUCTION

Retinoblastoma is the most common intraocular malignancy in children, with a reported incidence ranging from 1 in 15,000 to 1 in 18,000 live births.<sup>[1]</sup> It is bilateral in about 25–35% of cases.<sup>[2]</sup> The average age at diagnosis is 18 months, unilateral cases being diagnosed at around 24 months and bilateral cases before 12 months.<sup>[2]</sup> Retinoblastoma was associated with near certain death just over a century ago. Early tumor recognition aided by indirect ophthalmoscopy and refined enucleation technique contributed to an improved survival from 5% in 1896 to 81% in 1967. Advances in external beam radiotherapy in the 1970s, followed by the era of chemoreduction in the late 1990s, resulted in further substantial eye salvage.<sup>[2-5]</sup>

### WHERE DO WE STAND NOW?

In neglected or untreated cases, retinoblastoma can demonstrate extraocular spread primarily through optic nerve<sup>[6]</sup> and also through the sclera.<sup>[7]</sup> Though it is a rare clinical presentation in developed countries, ranging from 6.3 to 7.6%,<sup>[8,9]</sup> it is not an unusual feature in developing and underdeveloped world. Leal-Leal *et al.*<sup>[10]</sup> reported an incidence of 18% in a large multicenter study from Mexico. Kao *et al.*<sup>[11]</sup> from Taiwan reported the incidence of orbital retinoblastoma to be 36% in a large study. The incidence is even higher (around 40%) from Nepal where Badhu *et al.*<sup>[12]</sup> reported proptosis

to be the most common presenting feature of retinoblastoma.

Orbital retinoblastoma is one of the major contributors to mortality and carries a poor prognosis for life.<sup>[13-17]</sup> The presence of orbital invasion is associated with 10–27 times higher risk of metastasis when compared to cases without orbital extension.<sup>[18-20]</sup> The 5-year survival rates of orbital retinoblastoma has been reported to be 88% from the United Kingdom,<sup>[21]</sup> 91% from Japan<sup>[22]</sup> and 93% from the United States.<sup>[23,24]</sup> However, the mortality in developing countries is still high owing to late presentations compounded by socioeconomic factors, with the mortality reported as high as 50–90%.<sup>[12,17,25-27]</sup>

There is no proven definitive therapy or management protocol for orbital retinoblastoma. It continues to remain a challenging disease to treat because of its complex nature and usually various combination therapies are needed to achieve reasonable results. Multimodal therapies are probably the next step forward. There are numerous reasons for this, which are as follows:

- Systemic chemotherapy alone is unlikely to eradicate residual orbital disease.<sup>[28,29]</sup>
- Orbital exenteration alone is unlikely to achieve surgical clearance.<sup>[30,31]</sup>
- External beam radiotherapy is unlikely to prevent systemic metastasis.<sup>[32,33]</sup>
- Histopathologic evidence of viable tumor cells present even in phthisical eyes following neoadjuvant chemotherapy.<sup>[34]</sup>

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Based on the current evidence, as mentioned above, Honavar *et al.*<sup>[35]</sup> developed a treatment protocol comprising initial triple drug high dose chemotherapy (3–6 cycles) followed by appropriate surgery, orbital radiotherapy and an additional 12-cycle standard dose chemotherapy. In this series, six cases of orbital retinoblastoma without intracranial extension and systemic metastasis underwent the protocol as described above and the authors reported dramatic resolution of orbital involvement and a mean event-free survival of 36 months. Most of the eyes following chemotherapy become phthisical. The authors agree that their encouraging protocol needs validation and further studies are needed to know whether fewer cycles are as equally effective since there are concerns of the long-term effects of high dose chemotherapy.

## NEW FRONTIERS OF THE FUTURE

When reviewing the literature, one fact that stands out clearly is the increasing survival of patients with orbital retinoblastoma. Progress has been made and is continuing on all fronts including medical, surgical, diagnostic, genetic, social and rehabilitative.<sup>[36,37]</sup>

### Medical frontier

Multimodal therapies for advanced retinoblastoma are picking up pace and support from all spheres as amply elucidated in this review. Histopathologic evaluations of eyes following neoadjuvant chemotherapy for orbital retinoblastoma have further vouched for multimodal approaches.<sup>[34]</sup> The introduction of stem cell rescue along with high dose chemotherapy has added another dimension to the treatment of orbital retinoblastoma.<sup>[38,39]</sup> The Children's Oncology Group trials (COG trials), currently taking place, has made a great effort to standardize the treatment protocols worldwide. Their well-designed COG ARET 0321 trial of intensive multimodal therapy for extraocular retinoblastoma will probably lay to rest most of the confusion revolving around management protocols. Other areas being investigated include pharmacologic enhancement of radiotherapy, use of tumor cell targeting techniques, differentiating agents and immunotherapy.<sup>[40]</sup>

### Radiotherapy frontier

Advances in external beam radiotherapy for retinoblastoma with more precise control of the beam through better collimation and tighter isodose curves strongly argue in favor of its continuing supportive role in the management. The modern approaches that are being investigated include stereotactic conformal radiotherapy using a micromultileaf collimator, proton therapy using a fixed horizontal beam and tantalum localization or a rotating gantry with spot scanning.<sup>[41]</sup>

### Surgical frontier

Better survival has led to increasing research and advances on the surgical front. Newer implants with focus on orbital development and, hence, better cosmesis are coming up.<sup>[42]</sup>

Increasing developments in ophthalmology with focus on newer materials and techniques are leading to better implant retention and less exposures or extrusions.<sup>[43]</sup> Upcoming concepts in orbital reconstruction, particularly in children, and newer modalities like free tissue transfer for anophthalmic orbit syndrome may pave way for good cosmesis in patients of orbital retinoblastoma who undergo exenteration and radiotherapy.<sup>[44,45]</sup>

### Diagnostic frontier

On the diagnostic front, exploring the fetal eye is a new frontier. Fetal magnetic resonance imaging (MRI) and fetal three-dimensional ultrasound are being increasingly explored for prenatal diagnosis. The only two cases reported of *in utero* diagnosis using fetal ultrasound had massive extraocular extension.<sup>[46,47]</sup> MRI is also being increasingly used to study the biocolonization of the orbital implant.<sup>[48]</sup> Whole body bone scans using technetium-99, as shown by Kiratli *et al.*,<sup>[49]</sup> and fluorine-18 fluorodeoxyglucose positron emission tomography (PET CT), as demonstrated by Moll *et al.*,<sup>[50]</sup> reflect a glimpse of what possibly lies in store for early detection of metastasis.

### Genetic frontier

On the genetic front, there has been a distressingly little progress in spite of the fact that *RB1* was the first human cancer gene to be cloned. Development of an automated, inexpensive screening examination for *RB1* mutations has been a long-term need. However, recently, Parsam *et al.*,<sup>[51]</sup> from the authors group, have developed and published a combinatorial and less expensive approach for the detection of *RB1* mutations, which is likely to have applications as a screening tool. Ali *et al.*<sup>[52]</sup> have for the first time explored the possible correlations between different types of mutations on the *RB1* gene and clinical presentations. It is interesting to note that large deletions were found to correlate with extraocular extension and metastasis at presentation. Further efforts are needed to make it a routine part of patient care. There is also an increasing realization of using a different approach for patients at high risk of metastatic disease. Newer researchers have described a class of genes called the metastasis genes and the metastasis suppressor genes.<sup>[53-57]</sup> These genes affect the ability of cancer cells to establish growth foci in locations distant from the primary cancer but do not affect the primary tumor itself. The exploitation of these genes and the pathways to block the growth at distant sites holds promise for precisely targeted therapy to prevent metastasis.<sup>[58-60]</sup>

### Social frontier

On the social front, awareness through education and outreach to the community has helped to prevent delayed presentations and promote an early referral. Impact of educational programs in certain developing nations of Central America where it was linked with the vaccination programs is continuing to yield encouraging results with the rate of orbital retinoblastoma diagnosis reducing by almost half in the post-campaign period.<sup>[61,62]</sup> Similar programs could be cloned to developing

countries in Africa and southern Asia, specifically targeting the education of general population and primary care providers.

## CONCLUSIONS

Orbital retinoblastoma is no doubt still a huge challenge by itself. Although the survival has increased over the last few years, lack of access to medical facilities, lack of education about the need for early medical attention and cultural resistance to enucleation continue to contribute to an epidemic of extraocular disease at diagnosis in the developing world. Multimodal therapies and advancement on all fronts elucidated above appear as rays of light in a dark forest which is providing us with clues to a glittering light ahead to fight the darkness surrounding us at present. There is a definite hope that one day we will conquer this disease as we have conquered many others in the past.

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