FEATURE

Advances in the Management of Retinoblastoma

Written by Nicola Parry

Hans E. Grossniklaus, MD, Emory University School of Medicine, Atlanta, Georgia, USA, delivered the Jackson Memorial Lecture, in which he discussed the advances that have occurred in retinoblastoma (Rb) over the past 50 years.

Dr Grossniklaus noted that when Edwin P. Dunphy, MD, presented the Jackson Memorial Lecture in 1964, he referred to 4 periods in the history of Rb since the 18th century: prehistologic, histologic, enucleation, and irradiation/chemotherapy.

Since 1964, however, there has been an unprecedented rate of progress in research and treatment in Rb. Dr Grossniklaus proposed 3 additional stages of significant advances in this field, as represented by the periods of molecular biology, targeted therapy, and global health awareness.

MOLECULAR BIOLOGY

According to Dr Grossniklaus, increased knowledge of the genetics and molecular pathogenesis of Rb and mechanisms of its progression have been the most significant contributing factors to the advancement of understanding this tumor in the past 50 years.

During this period, Knudson's 2-hit hypothesis was a pivotal milestone that explained the relationship between hereditary and nonhereditary forms of Rb. In the hereditary form of the disease, which typically presents as bilateral with multiple tumors, the child inherits one mutation in the *RB* gene and then acquires a second mutation or hit. However, in the nonhereditary form, cells in the developing retina acquire both mutations. This form usually presents in children at a later age than in the hereditary form, typically arising as a single unilateral tumor.

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Dr Grossniklaus noted that additional events are now known to be required for Rb progression [Harbour JW. *Invest Ophthalmol Vis Sci.* 2006]. The Rb protein recruits additional proteins to binding sites related to transcription factor E2F, resulting in alterations in chromatin structure and preventing transcription from occurring. When Rb is phosphorylated by cyclin-dependent kinases, these proteins unbind, and histone is released from DNA. This allows transcription to proceed, thereby resulting in cell division and proliferation.

Dephosphorylation of Rb leads to cell exit, resulting in differentiation and senescence, and cell cycle exit can also occur in situations of cell stress or hyperproliferation. When Rb is hyperphosphorylated, E2F is released, and the cell undergoes p53-mediated apoptosis.

Dr Grossniklaus described the Rb protein as the "master regulator of the cell cycle." When mutations occur in both alleles of the *RB* gene, uncontrolled cellular proliferation or retinocytoma formation result, and additional events can occur that result in progression to Rb.

Advances have occurred in the pathology of Rb. High-risk histopathologic features have been identified, including optic nerve invasion beyond the lamina cribrosa, massive choroidal invasion in which the tumor is in contact with the sclera for ≥3 mm, and a combination of any optic nerve invasion and any choroidal invasion [Sastre X et al. *Arch Pathol Lab Med*. 2009].

Results from a recent molecular study showed that Rb can be classified on the basis of its cellular origin [Kapatai G et al. *Br J Cancer.* 2013]. Group 1 tumors arise in retinal precursor cells, expressing genes found in early retinal development, and group 2 tumors arise later in development from cone precursor cells, expressing genes found after cone development. These findings suggest that the tumor may be stratified by gene expression profile with regard to its clinical behavior and outcome.

Dr Grossniklaus indicated that recent work in his laboratory has examined the association between (1) tumor anaplasia—an apparent manifestation of the gene expression profile—and (2) the development of metastases and survival in patients with Rb [Grossniklaus HE. *Am J Ophthalmol*. 2014]. Tumors from 266 patients who underwent enucleation for unilateral Rb were

Figure 1. Relationship Between Degree of Tumor Anaplasia and Survival

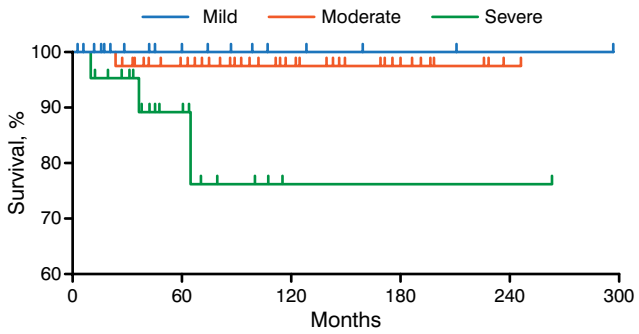

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Table 1. International Classification of Retinoblastoma

Group	General Features	Specific Features
A	Small tumor	Tumor ≤3 mm
B	Larger tumor	Tumor >3 mm
C	Focal seeds	Seeds ≤3 mm from retinoblastoma
D	Diffuse seeds	Seeds >3 mm from retinoblastoma
E	Extensive retinoblastoma	Retinoblastoma occupies >50% of globe

Source: Murphree AL. *Ophthalmol Clin North Am.* 2005.
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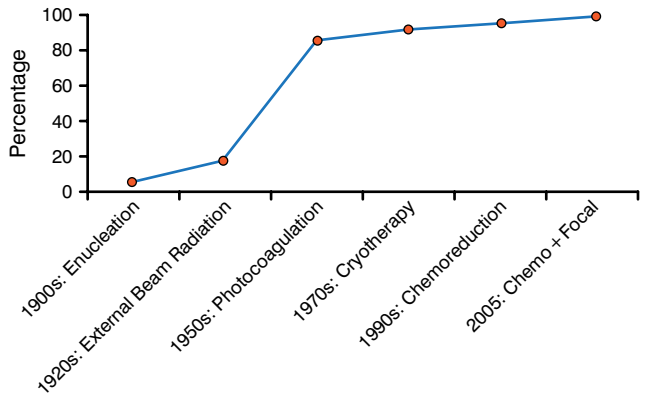
Figure 2. Five-Year Survival Rate in Developed Countries



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classified as retinocytoma or anaplasia (mild, moderate, or severe). The results of the study showed a significant correlation between anaplasia grade and survival, with patients with severe anaplasia being more likely to develop metastases or die when compared with those with mild or moderate grades ($P < .01$; Figure 1).

TARGETED THERAPY

Advances have been made in the treatment of Rb. According to Dr Grossniklaus, chemotherapy now includes the use of alkylating agents (eg, melphalan), platinum-based antineoplastic agents (eg, carboplatin), topoisomerase inhibitors (eg, etoposide), and vinca alkyloids (eg, vincristine). Chemoreduction for Rb involves intravenous injection of these agents plus focal consolidation of the regressed tumor with laser therapy or cryotherapy. He noted that these advances in globe-salvaging therapies led to the International Classification of Retinoblastoma staging system, which classifies the tumor based on its size and location as well as the presence and location of vitreous seeds (Table 1) [Murphree AL. *Ophthalmol Clin North Am.* 2005].

Dr Grossniklaus also discussed the use of intra-arterial chemotherapy as a successful treatment option for some patients. In this technique, a catheter is introduced into the opening of the ophthalmic artery, allowing injection of melphalan, topotecan, or carboplatin. Intravitreal chemotherapy has emerged as a safe and successful option, particularly in cases with recalcitrant vitreous seeds of Rb.

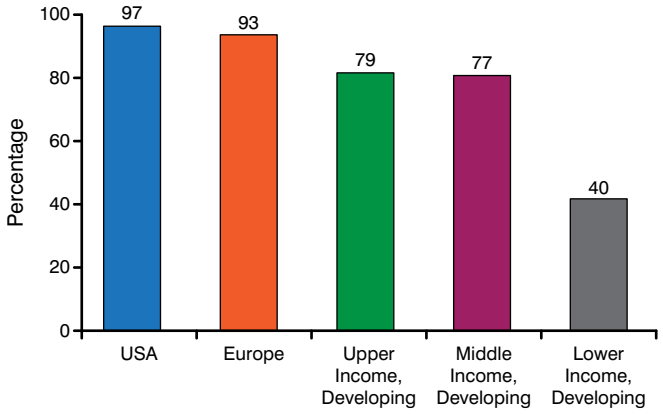
He indicated that work in his laboratory has centered on developing intraocular chemotherapy techniques via a rabbit xenograft model of human Rb [Kang SJ, Grossniklaus HE. *J Biomed Biotech.* 2011]. Additional work has involved the technique of suprachoroidal injection with a microneedle that facilitates injection into the suprachoroidal space, enabling delivery of chemotherapeutic agents into the posterior aspect of the eye without entering the vitreous space.

GLOBAL HEALTH AWARENESS

Dr Grossniklaus described Rb as a "remarkable success story." Despite being a once-fatal disease, the overall survival for Rb in developed countries has increased in the past 100 years due to significant advances in this field (Figure 2).

However, he emphasized that in the current era, global health awareness in Rb is increasing. Although up to 300 new cases of the tumor are diagnosed each year in the United States, >1000 new patients are identified with Rb

Figure 3. Comparison of 5-Year Survival Rates in Retinoblastoma



Source: Canturk S et al. *Br J Ophthalmol.* 2010.
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annually in China and India. Because the largest population growth in the coming years is projected to occur in Asia, most new cases of Rb will occur in this region [Shields C, Shields JA. *Curr Opin Ophthalmol.* 2006].

He shared data demonstrating that, although survival rates for Rb are high in the United States, they decrease to only 40% in developing countries with lower incomes (Figure 3) [Canturk S et al. *Br J Ophthalmol.* 2010].

The main challenge for the future in Rb is therefore a social one that involves ensuring that children in developing low-income regions across the world have access to adequate medical care, Dr Grossniklaus concluded.