The Management of Retinoblastoma

Running title: Management of Retinoblastoma

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Abstract

Retinoblastoma (Rb) is the most common primary intraocular malignancy of childhood, but an uncommon paediatric cancer, with a constant incidence worldwide of 1:15,000 - 1:20,000 live births. Despite its rarity, Rb has served as a cornerstone in the field of oncology in many of the aspects that comprise cancer management, including classification schemes, treatment modalities, genetic testing and screening of those with genetic risk. Until just over half a century ago, the major treatment for Rb was eye removal, and prognosis was poor with outcome fatal for most children. The dramatic evolution, in a very short period of time across all fields of Rb management, as well as the development of specialized Rb centres, better infrastructure and introduction of awareness campaigns, has resulted in nearly 100% survival in developed countries and allowed eye salvage in many of the cases, including advanced ones. External beam radiotherapy was used as the main treatment choice for over 4 decades, but replaced by chemotherapy at the turn of the century. Initially, and still in many centres, chemotherapy is administered by means of intravenous infusion, but recently is targeted directly into the eye by means of intra-ophthalmic artery chemotherapy and intravitreal chemotherapy. To date, a range of treatments is available to the Rb expert, including primary enucleation for advanced Rb, but there is lack of consensus in a number of scenarios as to what to use and when. In such a rare cancer, treatment outcomes are reported usually via retrospective analyses of case series, with few prospective randomized controlled trials. Classification schemes have also evolved following the introduction of new treatment modalities, but discrepancies exist among centres with respect to the preferred schema and its interpretation. Retinoblastoma management is a remarkable success story, but the future will require a collaborative effort in the form of multicentre randomized controlled trials in order to further improve the quality of care for this subset of young children with ocular cancer.
Introduction

Retinoblastoma (Rb) is a unique eye cancer that, despite its rarity, has previously and continues to serve as a benchmark for all oncology in terms of tumour diagnosis, classification and management. It was the first human cancer treated in the 1920s with an early attempt at brachytherapy and in the 1950s with a linear accelerator. It is initiated by a mutation in the RB1 gene, which was the first described tumour suppressor gene, in the 1970s and 1980s.¹⁻³ This year, it has become the first cancer for which a hereditary component was added to its AJCC TNM classification schema (i.e. TNMH).⁴ Rb is also a success story, one of the most prominent ones among all childhood cancers.⁵ A cancer with nearly 100% mortality a century ago now has over 98% survival in developed countries.⁶ It is an eye tumour that was treated just over half a century ago only by means of enucleation, but today in the appropriate scenario can be treated conservatively with retention of functional vision. This success is attributed to better understanding of the genetic basis of the disease, to establishment of specialist centres, primary care infrastructure and public awareness campaigns, and in no small measure, to the dramatic evolution of Rb management and treatment options over the last century.

Enucleation

Petrus Pawius from Amsterdam is credited for the first description of a tumour resembling Rb, in 1657.⁷ However, the first description of Rb as a distinct clinical entity, in 1809, is accredited to James Wardrop, a Scottish surgeon who practiced in London.⁷ Wardrop, prior to the introduction of the ophthalmoscope, was the first to state that the tumour arose from the retina, and the first to demonstrate its spread via the optic nerve, into the brain, and also to other parts of the body (i.e. distant metastasis). He is also credited for being the first to treat Rb with enucleation, before the introduction of general anaesthesia, in an attempt to save life. However, an attempt that failed in all cases treated by this approach. He was well aware that failure, resulting with death, was a result of late disease stage with involved optic nerve, and also that surgery in many instances had a palliative effect, but at the same time expedited the patient’s death. Following the introduction of chloroform for
general anaesthesia and first ophthalmoscope in 1851, enucleation became the treatment of choice for Rb. Enucleation surgery continued to evolve, but the first to suggest that a long optic nerve stump should be removed with the eyeball at the time of operation was Von Graefe,\textsuperscript{7} resulting with Improvement in survival rates soon after.\textsuperscript{8,9}

**From eye removal to preservation**

First attempts at conservative therapy by means of focal radiotherapy were explored in London in the 1920s by Foster Moore and Hyla Stallard at St. Bartholomew’s Hospital and Moorfields Eye Hospital.\textsuperscript{10,11} They used a radon seed that was surgically inserted into the tumour and left to decay. The daughter isotope is radioactive lead, so the eye remained radioactive and hence this technique was abandoned. Years later, plaque brachytherapy was developed by Stallard, using cobalt-60 applicators.\textsuperscript{12} The technique of plaque brachytherapy continued to evolve, but for Rb it was used only for selected cases.\textsuperscript{13} The paradigm shift to conservative therapy occurred in the 1950s and onwards with the development of the linear accelerator and introduction of external beam radiotherapy (EBRT) by Henry Kaplan from Stanford University. It was initially used in a Rb patient, successfully, resulting in eye salvage. Soon after, EBRT became the major treatment choice in most cases of intraocular Rb, whereas enucleation was reserved only for the most advanced ones with irreversible ocular damage. The advent of radiotherapy changed the perception of the cancer, and its management, from eye removal for survival to eye preservation, followed by the pursuit of retention of vision, though the order of priorities remained the same (i.e. the treatment paradigm for retinoblastoma: save life, preserve the globe, retain vision). Algernon Reese and Robert Ellsworth treated many patients with EBRT in New York City, and were able to predict the chances of globe salvage in a classification system that became eponymous.\textsuperscript{14} However, after nearly half a century of extensive use, it was recognized that radiation significantly increases the risk of developing a second malignancy in survivors of germline disease.\textsuperscript{15,16} EBRT was widely abandoned, replaced by chemotherapy as the primary treatment for intraocular Rb.

**Novel concepts in retinoblastoma genetics**
Carl Nordling, a Finnish-born statistician and cancer biologist, was the first to suggest in 1953, that cancer is caused by mutations that multiply and accumulate through large-scale proliferation of cells. Nordling proposed that at least 6 sequential mutations are a prerequisite for cancer to develop, a notion later rejected, but which set the basis for the two-hit cancer hypothesis, conceived 2 decades later, and which is still regarded a landmark. Alfred Knudson, an American physician and cancer geneticist, made population observations on hereditary and non-hereditary cases of Rb, suggesting in 1971 that cancer is caused by 2 mutational events. According to his theory, in hereditary Rb, 1 mutated allele is inherited by the offspring and thus the germline mutation exists in all cells of the body, whereas a second mutation occurs in somatic cells early in life. This disease form gives rise, usually, to bilateral multifocal Rb that presents at an early age (Fig. 1). In the non-hereditary disease form, both mutations occur sporadically in somatic cells, giving rise to unilateral unifocal Rb that presents at a relatively later age. Knudson later showed that this model was also applicable in Wilms’ tumour (i.e. nephroblastoma). His studies marked the conceptual shift from oncogene activation to tumour suppressor gene loss of function, as the cause of cancer. Using deletion, linkage and loss of heterozygosity studies, the mutated gene RB1, located on chromosome 13q14, was cloned in 1986. These findings enabled early genetic testing and diagnosis of children at risk of developing intraocular Rb. In addition, they led to the development of screening programmes, which resulted in earlier diagnosis of Rb, at an earlier tumour stage, requiring less aggressive treatments to reach tumour control, with better visual outcomes, fewer examinations under anaesthesia (EUA), and lower costs. Some have also suggested performing amniocentesis during pregnancy for embryos with a family history of Rb and preterm delivery in cases where the family’s RB1 mutant allele was found. However, this management approach remains under debate. More recently Brenda Gallie and colleagues investigated non-familial Rb tumours with no RB1 mutation, and found in this relatively small subgroup high rates of MYCN amplification, challenging the dogma that Rb is exclusively initiated by mutation in the RB1 gene.

Fig. 2A shows a pedigree of familial Rb. Three generations of affected patients representing the evolution of Rb management and beneficial impact of genetic studies and screening programs. In this family, where initial genetic testing was carried out by means of linkage
analysis, a mutation in exon 8, RB1 (LRG_517t1) c.751C>T, p.(Arg251*) was identified. It enabled cord blood examination during pregnancy to confirm the presence of the mutation in the grandchild. Screening EUAs soon after birth allowed early Rb diagnosis and tumour control by use of focal therapies only (Fig. 2B) and resulted with final visual acuity of 20/18 in both eyes after 76 months of follow-up.

Based upon the yield of the genetic tests performed in the London Retinoblastoma Service, a screening protocol was designed for patients in whom a blood RB1 mutation was found. We have recently analysed 169 Rb cases (229 eyes) that presented, were treated and monitored in our centre from 2005-2013 (unpublished data). Of these, 21 (14%) children had familial Rb, were found to have a blood mutation and initially diagnosed with the disease following screening EUAs. After a median follow-up time of 70 months (mean: 75; range: 19-141), only 50 patients had both eyes salvaged. However, a significant proportion of these were the familial cases (n=17 (34%)), supporting the concept of genetic testing and screening programs.

The chemotherapy era

Intravenous chemotherapy (IVC) in the 1990s was used for extraocular Rb, but Judith Kingston and colleagues from the London Retinoblastoma Service, recognized the possibility that IVC used in an autonomic nervous system tumour, neuroblastoma, could be extended to advanced intraocular Rb, with relative success, depending on tumour stage – an idea that gained favour worldwide. This marked another shift in the treatment paradigm, but there are variations in the drugs used (the commonest chemotherapeutic agents are vincristine, etoposide and carboplatin), the number of cycles and the addition of other focal (laser therapy) or systemic (cyclosporine) treatments. By 2005, it became apparent that the Reese-Ellsworth classification was not suitable for predicting the success of IVC. Linn Murphree from the Children’s Hospital of Los Angeles introduced the International Intraocular Retinoblastoma Classification (IIRC) to better predict Rb outcomes following IVC (Table 2). According to the IIRC schema, Groups A and B tumours are confined to the retina, Groups C and D show Rb seeding and/or retinal detachment, and Group E eyes, the
most advanced intraocular stage, show irreversible damage to ocular structures. Jerry and Carol Shields in Philadelphia showed that the IIRC predicted the salvage rates of the eye, finding that Groups A-C eyes were successfully managed with IVC and local treatments, with ≥90% tumour control rates; Group E eyes were primarily enucleated because of the risk of metastatic spread, whereas Group D eyes posed the biggest challenge for the Rb clinician with a 47% globe salvage rate (Fig. 3). While some favored enucleation of all Group D eyes, others attempted salvage by means of IVC and adjuvant therapies, achieving success in less than half of cases. During this era, treatment failure was resorting either to secondary enucleation or EBRT.

**Targeted chemotherapy**

Notwithstanding the great successes of systemic chemotherapy, Rb management continued to evolve, with two main drivers: to reduce systemic side effects associated with IVC and to increase salvage rate of more advanced intraocular Rb eyes. The era of targeted delivery of chemotherapy to the eye was born. Intra-ophthalmic artery chemotherapy (IAC) was introduced by Akihiro Kaneko and colleagues from Tokyo, and then developed further and popularized in early 2000s by David Abramson and colleagues in New York. The procedure, performed under general anaesthesia, includes puncture of the femoral artery by a 4-French catheter and anticoagulation with intravenous heparin. Following this, the catheter is guided into the internal carotid artery, a micro catheter is then inserted into the ophthalmic artery and chemotherapy injected into the eye. IAC results in a significantly higher drug concentration that reaches ocular structures, up to 250 fold more than after IVC. This technique requires the considerable expertise of an interventional radiologist and there was a learning curve, but cure rates were impressive with 85% of Group D treatment naïve eyes retained.

In other branches of ophthalmology and in other ocular cancers such as vitreoretinal lymphoma, diseases were being treated by means of intravitreal injection. For Rb the concern was tumour seeding outside the eye, and hence metastatic spread. Intravitreal chemotherapy (IVIC) was first introduced in Sweden, later developed in Japan and more
recently explored in Lausanne, Switzerland. In 2010s, Francis Munier and colleagues developed a safety enhanced technique for injecting chemotherapy directly into the vitreous cavity. The resulting high concentration within the target organ was successful in treating vitreous seeds, a notorious tumour component that could previously be treated only by EBRT or enucleation.

**Intravenous vs intra-arterial chemotherapy**

While IViC is utilized only as salvage therapy, in many centers IAC replaced IVC as first-line treatment. According to a recent survey of Rb centers, over 75% of unilateral Group D Rb cases are treated today with first-line IAC. A recent summary statement from 4 large Rb centers indicated that for unilateral Group D Rb, all use IAC as first-line therapy, some also for Group E eyes and for bilateral cases. However, surveys and summary statements are prone to practice preference and cannot replace robust prospective randomized clinical trials, which are lacking in the field of Rb research, comparing the efficacy and local and systemic safety of IVC versus IAC. It is not possible to tell whether one modality is superior and/or safer than the other.

Following IVC, for many years the reference number was 47% eye salvage rate for Group D Rb, as reported by Shields et al in 2006. Recently, our group published the outcomes of primary IVC for Group D Rb, in which at a median of 5 years follow-up, 63% of eyes were salvaged. In this report the replacement of EBRT by IAC for salvage was confirmed. For intraocular disease EBRT is considered to be akin to enucleation, though it still has importance in orbital disease which is usually seen in developing countries. Three recent retrospective non-randomized studies investigated the success rate of primary IAC for Group D Rb, and found it to be significantly higher in reaching tumour control (>85%) compared to IVC (comparison was to historical controls). However, the role of IViC as salvage in addition to IAC was not clear in all studies, precluding a clean comparison between the primary treatment modalities. Abramson et al. reported an 85% salvage rate for primary IAC for Group D Rb. Their study has several limitations, including short follow-up time for several of the patients. Patients receiving IViC were not included, though three
of the patients that received IAC as first-line developed metastatic disease, a higher rate compared to IVC. In comparison, in our study,\textsuperscript{44} over the course of 13 years, none of the patients treated with IVC has developed metastatic spread from intraocular disease. Yousef et al recently attempted to perform a meta-analysis to report the outcomes of IAC, but were limited as the relevant literature showed that none of the studies had a comparative group.\textsuperscript{47} Nevertheless, they found that 2% to over 3%, and possibly over 4% of patients treated by means of IAC have developed metastatic disease. In their review, they faced difficulties in data analysis associated with poor quality of the reviewed reports. However, if these are accurate figures, they do raise concern as to the safety of IAC for these patients, and paediatric oncologists will need to include these concerns in systemic screening strategies.

**Risk for metastatic spread**

The risk of metastatic spread from intraocular Rb is evaluated by histopathology analysis after an eye is enucleated. High-risk histopathology (HRH) features include spread of tumour to the optic nerve, choroid and/or anterior ocular structures (Fig. 4),\textsuperscript{48} warranting adjuvant IVC. Primary enucleation remains the treatment of choice for Group E eyes, with 24% of these that harbor HRH features.\textsuperscript{49} What about Group D eyes? Can a Group D eye harbor HRH features? Our group recently analyzed the histopathology of 40 such eyes that underwent primary enucleation, and indeed found HRH features in 13% of cases.\textsuperscript{50} In many centers, enucleation has been relegated to a diminishing role, so it is ironic that such a study on enucleated eyes helps to inform the debate regarding optimizing the choice of treatment in Group D eyes that are to be retained. The options of conservative treatment for these eyes is IVC, where intraocular and HRH or any micrometastatic disease are simultaneously treated, or IAC just to the affected eye, where the local tumour control rates are impressive but the potential for systemic disease remains more open. From enucleated eyes, we found that the absence of vitreous seeds at presentation was a bad prognostic sign that was associated with higher chance of harbouring HRH features. This sign can potentially serve as a clinical one, when deciding on the mode of primary treatment for a Group D eye, and especially when considering primary IAC.
Primary enucleation in the era of conservative chemotherapy

What then is the role of primary enucleation for Group D Rb? Does it have a place in the current era of systemic and targeted chemotherapy? We believe that it does, with the main advantage being a single procedure that cures the patient. In another retrospective analysis performed by our group, we evaluated all unilateral-presenting Group D Rb patients, and found that in a median time of approximately 5 years, only 1 out of 55 developed a new tumour in the fellow eye, and this single patient had familial Rb. We additionally quantified for the first time the burden of treatment in relation to the number of EUAs, especially as there has been some experimental work on neurological deficit in pediatric anesthesia. We looked at the number of EUAs in conservatively treated patients versus primary enucleation, finding that to retain an eye there were up to 3 times more EUAs compared to the primary enucleation group. These results can help to inform the choices for patients’ families and the option of primary enucleation can be offered, especially in unilateral cases with low visual potential in an older age group – not an uncommon finding with Group D disease.

Classification schemes for retinoblastoma

Reese and Ellsworth developed a classification system that predicted the chances for eye salvage following EBRT. Next was the IIRC (Table 1), developed by Murphree, and that was found to predict eye prognosis following IVC and adjuvant therapy. However, the latter classification was interpreted differently by different centers, mainly in regard to Group D and E eyes, affecting Group assignment in over 5% of eyes and 25% of Group E eyes. These discrepancies still exist today, making accurate comparison between different centers difficult. The AJCC classification system was developed by the American Joint Committee on Cancer. Since mid-20th century it classifies all cancer types according to the TNM (tumour, node, metastases) system. Recently, the 8th edition was published and for the first time included, only for Rb, a hereditary component (Table 2), defined as bilateral Rb, Rb with an intracranial CNS midline embryonic tumor, family history of Rb, or germline disease. The role and use, on a daily clinical basis, of the new TNMH classification remains to be proven.
Conclusions

The management of Rb has evolved significantly over the last century. Genetic testing and screening protocols have become common practice in many centers worldwide, improving significantly the quality of care for these patients. The Rb expert today has a large armamentarium to treat intraocular disease which includes chemotherapy administered through different routes of administration. The most crucial time point along the decision tree is at presentation, after the first EUA, when the various options for primary treatment are discussed with the patient’s family. In a rare cancer such as Rb, unfortunately most studies are retrospective. Although there is a need for prospective, randomized, multicenter, head to head controlled trials, to compare the various outcomes of primary IVC versus IAC, the reality is that such efforts will be hard to realize. Primary enucleation, a single straightforward surgical procedure that cures the patient, remains a valid treatment option that should be considered depending on the clinical scenario, but there is no doubt that Rb in the developed world has evolved to saving the eye and vision in a significant number of advanced cases, where previously these eyes were so often and routinely removed.
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**Figure Legends**

**Figure 1.** Bilateral multifocal retinoblastoma in a patient with germline disease. A detached retina and 2 tumour foci in the right eye (A), and 3 tumour foci in the left eye (B).

**Figure 2.** Pedigree of familial retinoblastoma (A). I2, born in the 1960s, developed bilateral retinoblastoma at the age of 8 months and was treated by means of enucleation of the right eye and cobalt-60 plaque brachytherapy in the left eye. II2 was born in the late 1970s, before genetic testing was available, developed bilateral retinoblastoma soon after birth, and was treated with external beam radiotherapy. *RB1* genetic testing was initially performed in the early 1990s through linkage analysis but a blood mutation was later identified: *RB1* (LRG_517t1) c.751C>T, p.(Arg251*), and confirmed in I2, II2, II3 and II5. Cord blood analysis performed for III1 in 2000s showed the presence of the mutation. Screening examinations in III1 started early after birth to find normal fundi in both eyes, initially (right (B) and left eye (C)). At the age of 3 months she developed bilateral multifocal disease; however that was successfully managed with focal therapies only. A small tumour focus (arrow) in the right eye, nasal to the optic disc, surrounded by oedematous retina immediately after cryotherapy (D), and in the left eye (E), 2 treated tumour foci, one immediately after cryotherapy and the second after the formation of a flat scar.

**Figure 3.** Retinoblastoma tumours, according to the International Intraocular Retinoblastoma Classification (IIRC), and response to treatments. A small retinal tumour supero-nasal to the optic disc, defined as Group A (A). The same tumour shown in (A) that has transformed into a pigmented scar after treatment with diode laser (B). Group B tumour (C) that has transformed into an inactive calcified lesion after intravenous chemotherapy (D). Group C tumour in the macular region, showing initial seeding (arrow; E). After intravenous chemotherapy the tumour has transformed into a calcified lesion/flat scar (F). Group D retinoblastoma showing diffuse vitreous seeding (G). Following intravenous chemotherapy the main tumour has regressed and calcified and remaining seeds treated
with intravitreal chemotherapy (H). Group E eye (I) showing a large retro-lental tumour that has seeded also into the anterior chamber (arrows). The main mass measured approximately 15x20mm by means of B scan ultrasound (J). The eye was also buphthalmic (expanded) and intraocular pressure was 35mmHg, hence it was enucleated.

**Figure 4.** Retinoblastoma high-risk histopathology features. (A) Retro-laminar optic nerve tumour invasion (arrows). (B) Tumour replacing the iris stroma and invading into the anterior chamber angle (arrows). (C) Massive choroidal invasion (Rb). (D) Massive choroidal (Rb) and scleral invasion (arrows).
Figure 2
Figure 3
Figure 4
# Table 1. International Intraocular Retinoblastoma Classification

<table>
<thead>
<tr>
<th>Group</th>
<th>Definition</th>
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| **A** | Very low risk.  
Eyes with small discrete tumors away from critical structures.  
All tumors are 3 mm or smaller, confined to the retina, and located at least 3 mm from the foveola and 1.5 mm from the optic nerve. No vitreous or subretinal seeding is allowed. |
| **B** | Low risk.  
Eyes with no vitreous or subretinal seeding and discrete retinal tumor of any size or location.  
Retinal tumors may be of any size or location not in Group A. No vitreous or subretinal seeding is allowed. A small cuff of subretinal fluid extending no more than 5 mm from the base of the tumor is allowed. |
| **C** | Moderate risk.  
Eyes with only focal vitreous or subretinal seeding and discrete subretinal tumors of any size and location.  
Any seeding must be local, fine and limited so as to be theoretically treatable with a radioactive plaque. Retinal tumors are discrete and of any size and location. Up to one quadrant of subretinal fluid may present. |
| **D** | High risk.  
Eyes with diffuse vitreous or subretinal seeding and/or massive, non-discrete endophytic or exophytic disease.  
Eyes with more extensive seeding than Group C. Massive and/or diffuse intraocular disseminated disease may consist of fine or “greasy” vitreous seeding or avascular masses. Subretinal seeding may be plaque-like. Includes exophytic disease and more than one quadrant of retinal detachment. |
| **E** | Very high risk eyes with anyone or more of the following:  
Eyes that have been destroyed anatomically or functionally by the tumor.  
Eyes with one or more of the following: irreversible neovascular glaucoma, massive intraocular hemorrhage, aspetic orbital cellulitis, tumor anterior to anterior vitreous face, tumor touching the lens, diffuse infiltrating retinoblastoma, phthisis or pre-phthisis. |
Table 2. 8th edition AJCC cTNMH Retinoblastoma Staging

### Definition of primary tumour (cT)

<table>
<thead>
<tr>
<th>cT</th>
<th>Definition</th>
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<tbody>
<tr>
<td>cTX</td>
<td>Unknown evidence of intraocular tumour</td>
</tr>
<tr>
<td>cT0</td>
<td>No evidence of intraocular tumour</td>
</tr>
<tr>
<td>cT1</td>
<td>Intraocular tumour(s) with sub-retinal fluid ≤ 5mm from the base of any tumour</td>
</tr>
<tr>
<td>cT1a</td>
<td>Tumours ≤ 3mm and further than 1.5 mm from the disc and fovea</td>
</tr>
<tr>
<td>cT1b</td>
<td>Tumours &gt; 3 mm or closer than 1.5 mm to the disc and fovea</td>
</tr>
<tr>
<td>cT2</td>
<td>Intraocular tumour(s) with retinal detachment, vitreous seeding or sub-retinal seeding</td>
</tr>
<tr>
<td>cT2a</td>
<td>Sub-retinal fluid &gt; 5 mm from the base of any tumour</td>
</tr>
<tr>
<td>cT2b</td>
<td>Tumours with vitreous seeding and/or sub-retinal seeding</td>
</tr>
<tr>
<td>cT3</td>
<td>Advanced intraocular tumour(s)</td>
</tr>
<tr>
<td>cT3a</td>
<td>Phthisis or pre-phthisis bulbi</td>
</tr>
<tr>
<td>cT3b</td>
<td>Tumour invasion of the pars plana, ciliary body, lens, zonules, iris or anterior chamber</td>
</tr>
<tr>
<td>cT3c</td>
<td>Raised intraocular pressure with neovascularization and/or buphthalmos</td>
</tr>
<tr>
<td>cT3d</td>
<td>Hyphema and/or massive vitreous hemorrhage</td>
</tr>
<tr>
<td>cT3e</td>
<td>Aseptic orbital cellulitis</td>
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<tr>
<td>cT4</td>
<td>Extraocular tumour(s) involving the orbit, including the optic nerve</td>
</tr>
<tr>
<td>cT4a</td>
<td>Radiological evidence of retrobulbar optic nerve involvement or thickening of the optic nerve or involvement of the orbital tissues</td>
</tr>
<tr>
<td>cT4b</td>
<td>Extraocular tumour clinically evident with proptosis and orbital mass</td>
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### Definition of regional lymph nodes (cN)

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<tr>
<th>cN</th>
<th>Definition</th>
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<tr>
<td>cNX</td>
<td>Regional lymph nodes cannot be assessed</td>
</tr>
<tr>
<td>cN0</td>
<td>No regional lymph nodes involvement</td>
</tr>
<tr>
<td>cN1</td>
<td>Evidence of preauricular, submandibular, and cervical lymph node involvement</td>
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### Definition of distant metastasis (M)

<table>
<thead>
<tr>
<th>cM</th>
<th>Definition</th>
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<tbody>
<tr>
<td>cM0</td>
<td>No signs or symptoms of intracranial or distant metastasis</td>
</tr>
<tr>
<td>cM1</td>
<td>Distant metastasis without microscopic confirmation</td>
</tr>
<tr>
<td>cM1a</td>
<td>Tumour(s) involving any distant site (e.g. bone marrow, liver) on clinical or radiological tests</td>
</tr>
<tr>
<td>cM1b</td>
<td>Tumour involving the central nervous system on radiological imaging (not including trilateral retinoblastoma)</td>
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<tr>
<td>pM1</td>
<td>Distant metastasis with microscopic confirmation</td>
</tr>
<tr>
<td>pM1a</td>
<td>Histopathological confirmation of tumour at any distant site (e.g. bone marrow, liver, or other)</td>
</tr>
<tr>
<td>pM1b</td>
<td>Histopathological confirmation of tumour in the cerebrospinal fluid or CNS parenchyma</td>
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**Definition of heritable trait (H)**

<table>
<thead>
<tr>
<th>HX</th>
<th>Unknown or insufficient evidence of a constitutional $RB1$ gene mutation</th>
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<tbody>
<tr>
<td>H0</td>
<td>Normal $RB1$ alleles in blood tested with demonstrated high sensitivity assays</td>
</tr>
<tr>
<td>H1</td>
<td>Bilateral retinoblastoma, retinoblastoma with an intracranial CNS midline embryonic tumour (i.e. trilateral retinoblastoma), patient with family history of retinoblastoma, or molecular definition of constitutional $RB1$ gene mutation</td>
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