National Retinoblastoma Strategy Canadian Guidelines for Care

INTRODUCTION

Retinoblastoma (Rb) is a rare and unique cancer that forms in the eyes of children, often before they are born. It is a complicated disease triggered by genetic mutations in one or more cells of the retina. The incidence of Rb is 1 in 15,000 live births,[1] with about 23 children being diagnosed in Canada each year. Untreated, Rb is fatal.

With timely screening, diagnosis, referral, treatment, and follow-up delivered in a systematic way by a multidisciplinary team, 98%[2-4] of children with Rb are cured, many with useful vision.[5] Canadian scientists are world leaders in the development of treatment and genetic analysis, yet many Canadian Rb families do not receive optimal care, due to inadequate knowledge of Rb in primary care settings, and wide variations in access to care. Early diagnosis is key to a successful outcome.

Access to care is one of the most difficult issues that Rb families must overcome. Specialists in Rb are available in only a few centres of excellence, so a patient's province of residence significantly affects access to high-quality Rb care. Variation in quality of care and access to care exposes Rb families to unnecessary risks, currently most evident as delay in diagnosis and unequal access to genetic testing. Most families are required to travel, some great distances, to receive appropriate care. However, not all provinces cover the costs associated with travel necessary to access care unavailable in the home province.

These challenges prompted the Canadian Retinoblastoma Society (CRBS) (a registered charity dedicated to addressing the needs of families who are affected by Rb), Rb families, and Rb experts from across the country to create the National Retinoblastoma Strategy (NRbS). The NRbS began as a discussion around the divergence in levels of care available across Canada. These guidelines form an integral part of that Strategy, as we meet our goal of ensuring every Canadian family impacted by the disease receives high-quality Rb care. These guidelines were created as a result of a unique partnership between experts in the fields of ophthalmology, oncology, genetics, social work, nursing, and other specialties from across Canada, as well as Rb survivors and their families. Together this group identified shortcomings in the Canadian healthcare system that result in less-than-optimal care being delivered to Rb families, and highlighted a national solution.

By agreeing upon and adopting a set of national guidelines, it is hoped that all affected families will benefit from a more standardized approach, delivering a broad spectrum of specialist treatment according to an agreed-upon guideline document that is evidence-based where possible. Furthermore, this approach will facilitate data collection and the application of scientific methods to the disease and its treatment.

METHODOLOGY

Through consultation and personal communications between key stakeholders from across Canada, the National Retinoblastoma Strategy (NRbS) emerged as a novel approach to address inequalities evident for children with Rb and their families across the wide geography and jurisdictions of Canada. The core of the Strategy was identified to be comprehensive patient-centred and family-centred guidelines, developed using the best available evidence and expert opinion for screening, diagnosis, treatment, and follow-up of Rb, and extending to broader needs, including geographical access to care, psychosocial resources for families, and health services with specific Rb expertise. As a first step, the Canadian Retinoblastoma Society (CRBS) undertook overall responsibility for the development of the *Canadian Guidelines for Retinoblastoma Care*. Future public and professional education will be based on these guidelines, and long-term feedback on their effectiveness will be assessed through measurement of outcomes for Canadian families.

Guideline Development

Where possible, the content of this document was developed in accordance with the Canadian Medical Association *Handbook on Clinical Practice Guidelines*[6] and criteria specified in the 6 domains of the *Appraisal of Guidelines Research and Evaluation (AGREE) Instrument*.[7] These domains cover the following dimensions of guidelines: scope and purpose, stakeholder involvement, rigour of development, clarity and presentation, applicability, and editorial independence.

The objective of this document is to guide Canadian healthcare professionals and assist them to maximize early detection of Rb, improve access for families to a Canadian standard of care, and eventually minimize risk and optimize patient outcomes. To meet this objective, the Expert Committee which drafted this document included healthcare professionals, researchers and paramedical staff with expertise in the areas of screening, diagnosis, treatment, genetics,

psychosocial support, and follow-up, as well as Rb survivors and family members (see "Committee List"). Each author group identified the key clinical questions in their area, and undertook a comprehensive literature search to establish the evidence base for their topic and develop recommendations. In large part because it is a rare disease, Rb children have not benefited from the kinds of clinical trial research that has profoundly improved outcomes of pediatric cancer in general.[8,9] No randomized clinical trials have been completed to assess clinical care of Rb.

Health benefits, risks and side effects of interventions were considered in formulating the recommendations. References used to support recommendations were evaluated according to criteria adapted from other published guidelines (Table 1).[10,11] However, as discussed above, in the absence of high-quality evidence in the field of Rb research, many of the recommendations were, by necessity, based on consensus. Throughout the development of these guidelines, the Expert Reviewers (see "Committee List") were consulted for their input and critique. All recommendations were reviewed by and approved by the Expert Committee. In the event of disagreement regarding wording, the consensus recommendations were reworked until all Steering and Expert Committee members were in agreement.

A draft version of the full document was reviewed by the International Expert Reviewers (see "Committee List"). Revisions were incorporated where relevant.

Disclosures

Funding for the development of the guidelines was provided by: Childhood Cancer Foundation, Candlelighters Canada, the Pediatric Oncology Group of Ontario, and the Canadian Ophthalmological Society. All committee members were volunteers and received no remuneration or honoraria for their participation in the guideline development process. Funding for translation of the guidelines from English to French was provided by the Canadian Ophthalmological Society. Funding for printing and dissemination of the guidelines was provided by a grant to the CRBS by the Institute of Human Development, Child and Youth Health and the Knowledge Synthesis and Exchange Branch of the Canadian Institutes of Health Research. All members declared they had nothing to disclose regarding any relationships with industry or other organizations.

Table 1. Criteria for assigning a level of evidence to recommendations

Level of evidence	Criteria
1	Randomized controlled trials (RCTs) (or meta-analyses) *without* important limitations
2	RCTs (or meta-analyses) *with* important limitations
	Observational studies (non-RCTs or cohort studies) with overwhelming evidence
3	Other observational studies (prospective cohort studies, case-control studies, case series)
Consensus	Inadequate or no data in population of interest
	Anecdotal evidence or clinical experience
	100% agreement of Steering & Expert Committee members

Guideline Updates

A process to update the guidelines will commence within 3 years of publication of this version and will establish a 5-year cycle of guideline reassessment, in terms of new literature and studies, and renewed consensus. Updates may be published in the event of significant changes in evidence supporting the recommendations.

Notes to Readers

These guidelines are based on the best available evidence and expert opinion, and are intended to optimize patterns of clinical practice. They are not to be prescriptive or replace clinical judgement,[6] nor restrict innovation. Healthcare professionals must always consider the needs, preferences, values, financial and personal circumstances of individual patients and work within the realities of their healthcare setting. Inequities in staffing, financial, equipment, and healthcare resources in different jurisdictions may impact upon physician and patient options and decisions. As the general nature of guidelines cannot provide individualized guidance for all patients in all circumstances, this document should not be used as a legal resource.[6]

SCREENING

Introduction

Early detection and immediate referral of children with retinoblastoma (Rb) increases the possibility of saving lives and eyes, and preserving useful vision. Vision screening in babies and children at appropriate ages and intervals, and screening of babies' eyes, may identify tumours at earlier stages, when more treatment options are available and the chance of cure is high. Moreover, healthcare costs are reduced, resources are redirected to high-risk patients, and unnecessary clinic visits and worry for unaffected family members are eliminated. The general population risk of developing Rb is approximately 1 in 15,000 live births.[1]

This chapter will highlight the presenting signs and symptoms of Rb, and delineate an examination schedule to screen children for eye problems, intended to improve early detection of Rb in Canada.

Common Presentations of Retinoblastoma

Reviews of 100 Rb cases in the United Kingdom (UK)[12] and 1654 in the United States (US)[13] showed that the most common presenting signs are **leukocoria** (white pupil) and **strabismus** (Table 2). Both exotropia (eye turned outward, temporal) or esotropia (eye turned inward, nasal) can be presenting signs for Rb. Less frequent signs are **changes in**

Table 2. Common presentation of retinoblastoma (based on Goddard et al.[12] and Abramson et al.[13])

Presentation	% of cases [12]	% of cases [13]
Leukocoria	52	54
Strabismus	29	19
Change in Eye Appearance	10	5
Reduced Visual Acuity	9	4

eye appearance, such as heterochromia or red, painful, or watery eyes, or a change in the child's behaviour that indicates **reduced visual acuity** (e.g., not fixing or following in infants, clumsiness in ambulatory children). In the United States, a known family history of Rb resulted in early clinical surveillance for only 5%, who had a higher ocular survival rate than those with no family history, or those with family history who did not choose early clinical surveillance. Today, the standard of care is molecular diagnosis to identify infants at risk in each family (see "Genetic Analysis" chapter).

The ocular survival rate is significantly lower when the presenting sign is leukocoria (8.5% over 5 years), rather than strabismus (17% over 5 years).[13] These results are similar to previous studies conducted in the US and other countries.[14-17]

Other Causes of Leukocoria and Strabismus

Conditions other than Rb can give rise to leukocoria, and also require management by an ophthalmologist: congenital cataract, persistent fetal vasculature, retinopathy of prematurity (ROP), coloboma, Coats' disease, toxocariasis, uveitis, and less well-known conditions such as Norrie disease. Some of these conditions may be diagnosed by routine screening (e.g., ROP screening in the premature baby population), and many require prompt treatment (e.g., a dense congenital cataract requires early extraction for optimal prognosis).[18,19]

Flash Photography Often Detects Photoleukocoria

Photoleukocoria is evidence of leukocoria on a flash photograph, observed as a white reflection in the eye, instead of the usual "red-eye reflex." Many parents now notice the white reflex in family photographs and then seek medical attention. Often, parents today first learn about Rb on the internet, searching for information about the strange appearance in their child's photograph. Photoleukocoria is most often observed when children with Rb are photographed in dim light (usually indoors) using flash and with the red-eye reduction feature turned off. Though the presence of leukocoria is not diagnostic of Rb, it warrants urgent clinical examination by a medical professional, and Rb is the most serious diagnosis.

Clinical Examination for Possible Retinoblastoma

Red reflex test to detect leukocoria

In several surveys of US pediatricians, 94–98% of pediatricians self-report that they routinely use the red reflex test, yet studies show that more cases of Rb are first noticed by parents, not physicians.[13,20] This could be due to the simple fact that family interacts with the child more often and has more opportunity to observe the child's eyes in various lighting and from different angles. It is essential that the red reflex test be performed correctly. Additionally, if the test is only performed in straight-ahead gaze, peripheral tumours might not be detected. Table 3 indicates the correct method for performing a red reflex test.

Hirschberg test to detect strabismus

A longer referral lag time was observed for patients presenting with squint/strabismus (median 7 weeks, range 1–80 weeks) than for leukocoria (median 1 week, range 1–48 weeks), decreased visual function (median 2 weeks, range 1–22 weeks), or change in eye appearance (median 1 week, range 1–8 weeks).[13] This suggests that physicians don't immediately recognize strabismus as a sign that might indicate the need for urgent care. However, making a referral for Rb on the basis of a presenting sign of strabismus is difficult, since misalignment is quite common, observed in 50% of normal infants younger than 1 month old.[21] However, the widespread opinion that strabismus is frequently observed in infants up to 6 months of age and will resolve itself is incorrect.[12]

The Hirschberg test, when performed correctly, is an accurate test of misalignment of the eyes of >10 prism diopters (Table 4). The age at which 90% of infants tested have aligned eyes ranges from 4 to 12 weeks.[22,23] Slight misalignments are common in infants younger than 1 month old, and small angle or intermittent misalignment is likely to resolve before the age of 3–4 months. However, large misalignments are not common or likely to resolve, and should be referred to ophthalmology. A rare but very serious cause can be Rb.

Vision Screening Guidelines

Regular infant vision screening could result in earlier detection of Rb. A review of major Canadian and American pediatric and vision health association vision screening guidelines[33-42] revealed that only the Canadian Paediatric Society (CPS) explicitly mentioned exploring for signs of Rb through regular eye screening from birth to 5 years of age in their 1998 version of their recommendations, reaffirmed in 2007.[43] Though the 2009 version does not specifically

Table 3. Correct performance of the red reflex test (adapted from Abramson et al.[13])

1. In a darkened room (to maximize pupillary dilation), a direct ophthalmoscope is focused on each pupil individually, 50 cm away from the eye. The red reflex obtained from each pupil is observed. It is useful to set the ophthalmoscope on +4 diopter setting for a focused image of the red reflex.
2. After each eye has been assessed separately, the eyes are viewed together with the child focusing on the ophthalmoscope light (Bruckner test) at a distance of 1 m. Any asymmetry in pupil colour, brightness or size warrants a referral. A white reflex is an ominous sign that warrants an urgent referral to an ophthalmologist to rule out Rb. (It should be noted that if the child is looking 15 degrees nasal to the path of the viewer, the optic nerve head can cause leukocoria, resulting in a false positive red reflex test.[24])
3. Dilated direct ophthalmoscopic examination may improve the ability to detect early Rb.[25] One drop of 0.5% cyclopentolate and one drop of 2.5% phenylephrine placed in both eyes 20–40 minutes before the red reflex test should provide an adequate pupillary dilation in those children with smaller resting pupil diameters.

Table 4. Conducting the Hirschberg test correctly[26–32]

1. A penlight or ophthalmoscope light is held approximately 25–40 cm from the child and the position of the corneal reflections is estimated.
2. Corneal reflections usually appear slightly nasally, compared with the centre of the pupil.
3. An asymmetry between the 2 eyes in the position of the reflections denotes misalignment.

mention Rb[44], the CPS is still the only organization, to our knowledge, to recommend eye examination from 6 months to one year of age, the ideal time to detect Rb, as most cases present around 1.5–2 years of age (Table 5). Since many children are not seen by pediatricians who are members of the CPS, but by other medical professionals such as family and general practitioners, we reiterate the CPS guidelines.

SCREENING—RECOMMENDATIONS

1. We recommend that all infants and children in whom someone has observed a white pupil (either in person or in a photograph) have a full dilated-eye examination including red reflex test within 72 hours by an ophthalmologist or medical practitioner who is fully aware of the importance of leukocoria as a sign of Rb [*Consensus*].
2. We recommend that any child with strabismus or suspected strabismus be seen by the child's pediatrician or family doctor:
   a. We recommend that the red reflex test be applied to any child with strabismus or suspected strabismus [*Consensus*].
   b. We recommend urgent referral (within 72 hours) to an ophthalmologist of any child with strabismus or suspected strabismus and an abnormal red reflex [*Consensus*].
   c. We recommend that appointments with ophthalmology or tertiary Rb centres should be given within 72 hours for the above signs of abnormality, which constitutes an emergency (see "Referral and Diagnosis" chapter) [*Consensus*].
3. We support the recommendations of the Canadian Paediatric Society[44] with respect to the suggested timing of vision screening for the general population [*Consensus*].

Table 5. Vision screening guidelines from the CPS[44]

Age	Screening Guideline
Newborn to 3 months	A complete examination of the skin and external eye structures including the conjunctiva, cornea, iris, and pupils.
	An inspection of the red reflex to rule out lenticular opacities or major posterior eye disease.
	Failure of visualization or abnormalities of the reflex are indications for an urgent referral to an ophthalmologist.
	High-risk newborns (at risk of retinopathy of prematurity and family histories of hereditary ocular diseases) should be examined by an ophthalmologist.
6 to 12 months	Conduct examination as above.
	Ocular alignment should again be observed to detect strabismus. The corneal light reflex should be central and the cover-uncover test for strabismus normal.
	Fixation and following a target are observed.
3 to 5 years	Conduct examination as above.
	Visual acuity testing should be completed with an age-appropriate tool.
6 to 18 years	Screen as above whenever routine health examinations are conducted.
	Examine whenever complaints occur.

All children should be screened in their preschool years for amblyopia or its risk factors, as well as for ocular diseases that may have serious consequences, such as Rb and cataracts. It remains the responsibility of the child's pediatrician to ensure that these tests are performed by the most qualified personnel.[43]

FEATURES AND CLASSIFICATION OF RETINOBLASTOMA CENTRES

Introduction

Since retinoblastoma (Rb) is so rare, it is important that the few new Canadian Rb diagnoses each year be managed by multidisciplinary teams that have the necessary resources and extensive ongoing experience in treating and managing patients with Rb. In this chapter, human resources, equipment, and facilities needed for optimal care of Rb in Canada are outlined. The recommended and mandatory resources (i.e., expertise of healthcare professionals, service delivery, equipment, and human resources) are defined for primary, secondary, or tertiary level Rb centres. Each level plays a significant and unique role in ensuring effective and timely referral, and management of Rb patients and their families as close to home as possible to still achieve optimal outcome.

Primary Healthcare

Typically, parents or healthcare professionals, such as family doctors and pediatricians, first note signs or express suspicion of Rb. Today, parents often search the internet and identify signs they have noted in the child to be consistent with Rb. These parents sometimes bypass their primary healthcare provider altogether, opting instead to take their child to a hospital emergency room. Rarely, primary healthcare professionals, including family doctors, pediatricians, optometrists or community-based ophthalmologists, first notice Rb during well-baby screening procedures. More often, parents bring their observations and even their concerns about the signs of possible Rb in their child to the attention of their primary caregivers. Primary healthcare professionals need to be aware of a family history of Rb and to recognize the need to refer such children urgently for assessment and surveillance.

Retinoblastoma Centres

Since the care of children and families with Rb is complex and the disease is rare, specialized centres are distributed across Canada, where expertise is focused. The complex treatment required to achieve good outcomes is best delivered in such centres. We list the human and physical resources that can optimize care of children with Rb and their families. We summarize the suggested resources for secondary and tertiary Rb centres (Fig. 1).

Personnel

Ophthalmic specialist

An ophthalmologist and (or) retinal specialist in the community may confirm the diagnosis of the primary referring doctor/centre. They can suggest the International Intraocular Retinoblastoma Classification (IIRC) (see "Treatment" chapter) of disease severity[45] that applies to each eye, and flag any risk factors for spread of tumour outside the eye.

Retinoblastoma specialist

A pediatric ophthalmologist, retinal specialist or ocular oncologist (and sometimes more than one, working as a team) with specific experience in the management of Rb will manage the ongoing care of children with Rb.

The primary treatment for unilateral Rb is removal (enucleation) of the affected eye. A surgeon with special interest in Rb will know the process for harvesting tumour for genetic studies after removal of the eye.

Specific training in overall management of Rb will include knowledge about and experience with focal therapy.

Pediatric oncologist and radiotherapist

A pediatric oncologist(s) dedicated to the treatment of Rb patients will participate in the care and lead management when chemotherapy is required. They will evaluate cerebrospinal fluid (CSF) and bone marrow when the child is at risk for metastatic disease. The oncologist actively recruits patients who need chemotherapy to suitable multicentre clinical trials, as available. A radiotherapist will become part of the team when required.

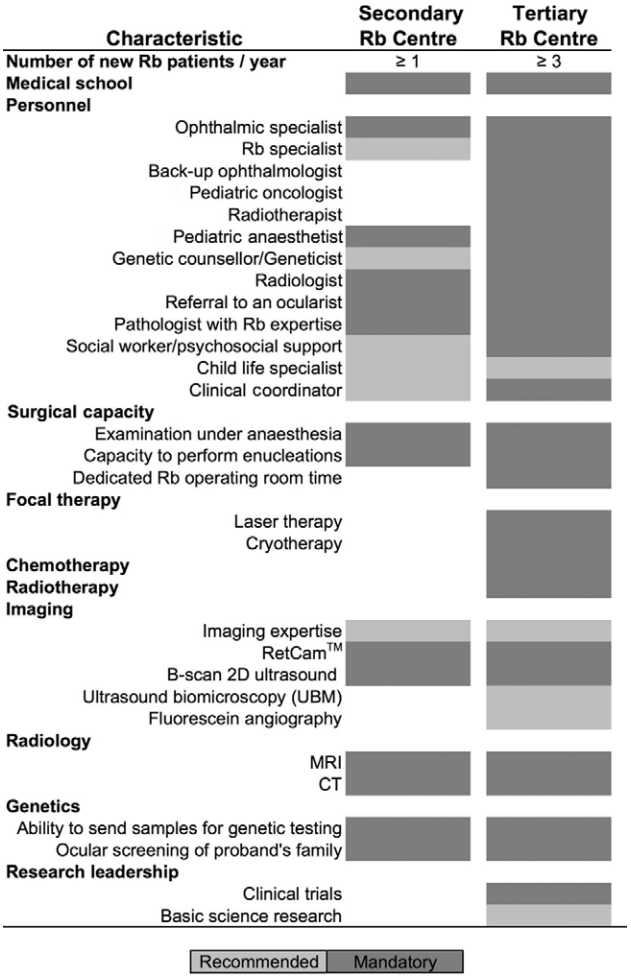

Figure 1–Optimal staffing and resources for secondary and tertiary Rb centres.

Pediatric anaesthetist

The pediatric anaesthetist is also a key team member since Rb patients need frequent examinations under anaesthesia (EUAs). Familiarity with one or more anaesthetists reduces parental and child's anxiety and facilitates smoother functioning of OR lists.

Geneticist and genetic counsellor

The geneticist (a physician with specialization in genetics) works with the genetic counsellor (paramedical staff) to provide clinical genetic services for Rb patients and families.

Radiologist

The availability of an experienced radiologist to interpret MRI and (or) CT images upon presentation and follow-up (see "Treatment" and "Follow-up" chapters) is vital.

Ocularist

An ocularist is an eye-care professional who makes and fits custom prosthetic eyes. When the socket has healed after enucleation, the ocularist takes an impression mould of the eye socket and creates the prosthesis to match the other eye for optimal cosmetic appearance. The ocularist also helps patients and parents learn to handle the eye and keep it clean.

Pathology

An ocular pathologist will fully evaluate the optic nerve, sclera, choroid, and anterior segment for evidence of risk of tumour spread outside the eye. Laboratory personnel should be experienced and comfortable with handling globes (eyes). Timely fixation and preparation of pathology slides of the enucleated eye are important for pathological confirmation of the diagnosis and evaluation of risk of extraocular extension.

Similar expertise is required to evaluate CSF and bone marrow for metastatic disease in children at risk.

Social worker/Psychosocial support

A specifically dedicated social worker helps Rb families cope with the emotional and financial implications of a new cancer diagnosis, providing counselling to facilitate coping with the crisis, adjustments, support and resource management, and education about Rb and the treatment process. Psychosocial support includes palliative care and bereavement support for end-of-life patients and their families respectively (see "Psychosocial Care and Access to Services" chapter).

Child life

Child life is specialized psychological support focusing on the distinct needs of young patients, and promotes effective coping skills and optimum development through play, preparation, education, and self-expression activities that are based on natural child development. A child life specialist is useful as a full participant in the multidisciplinary Rb

team, although today this key component may not be available outside major oncology centres.

Institutional support for multidisciplinary retinoblastoma team

Institutional support enables efficient functioning of a multidisciplinary retinoblastoma team, especially in centres that manage many Rb patients. For example, such centres will have dedicated operating room time specifically for Rb children, and team resources to promote long-term support for families.

Examination under anaesthesia

Full dilated-eye examination to detect (and treat) tumours in infants and young children requires the administration of a general anaesthetic. The timely availability of operating room staff for examination under anaesthesia (EUA), including nurses and anaesthesiologists, is standard for Rb centres.

Focal therapy

Laser therapy

Most centres use transpupillary 532-nm or 810-nm lasers through the indirect ophthalmoscope in the management of Rb tumours. The 1064-nm laser is useful for thick and recurrent tumours after chemotherapy. Both the infrared lasers (810 nm and 1064 nm) can also be delivered trans-sclerally.

Cryotherapy

Cryotherapy is used to treat tumours anterior to the equator of the retina or to increase access of chemotherapeutic drugs into the vitreous (pre-chemotherapy cryotherapy)[46] (see "Treatment" chapter).

Chemotherapy

Many pilot studies of chemotherapy to treat Rb have been reported, but have yet to be validated by randomized controlled trials.[47] Treatment of bilateral Rb currently involves chemotherapy with carboplatin, etoposide, and vincristine, with or without additional cyclosporine A. Medical staff (including oncologists, nurses, and pharmacists) experienced in the use of these drugs for treatment of Rb supervise this therapy (see "Treatment" chapter).

Radiotherapy

Radiotherapy is not commonly used now for primary treatment of Rb. When other means of saving the last remaining eye have failed, external beam radiation (EBR) may be given, preferably with modern precision to minimize dose to bone. Radioactive plaque therapy (brachytherapy) is occasionally useful for specific primary or recurrent focal tumours.

Ocular imaging

The wide-angle digital retinal camera, RetCam™, has become standard in Rb treatment centres worldwide to capture high-resolution images of the posterior and peripheral retina in children for sequential comparison of tumour progression or regression over time. Scleral depression, in combination with RetCam™ imaging, allows documentation of tumours up to the ora serrata. When used by an experienced imaging specialist, the RetCam™ can better detect Rb tumours at an early stage, when treatment required is minimal, than the indirect ophthalmoscope. Fluorescein angiograms with the RetCam™ reveal areas of tumour vascularization. Regular B-scan 2D ophthalmic ultrasound is an important tool to document intraocular calcification as strong evidence supporting a diagnosis of Rb. High frequency ultrasound such as ultrasound biomicroscopy (UBM) is particularly useful to assess anterior disease behind the iris, where it cannot otherwise be observed. Often the clinicians operate the imaging tools, but some centres employ imaging specialists who contribute valuable expertise to the team. The digital capture capability of the RetCam™ and ultrasound devices allows ophthalmologists to overcome distance, and easily consult with each other in difficult or challenging cases through telemedicine.

Radiology

The characteristic calcification within the Rb tumour is well detected by the widely available B-scan 2D ocular ultrasound. While computed tomography (CT) has previously been widely used in assessing eyes with large tumours for extraocular disease, it is now recognized that the radiation dose delivered by CT scan may increase risk of secondary non-Rb malignant neoplasms in children with *RB1*$^{+/-}$ germline mutation (see "Genetic Analysis" chapter).[48,49] Magnetic resonance imaging (MRI) of the head and orbits is therefore now preferred to image Rb upon presentation due to increased image resolution and avoidance of radiation, although it is generally less easy to access. MRI of the head and orbit confirms the Rb intraocular tumour, evaluates the extent of the Rb and screens for trilateral intracranial tumour.[50,51]

Genetic counselling

Rb-specific genetic counselling requires detailed knowledge of the biology of Rb and the interpretation of *RB1* mutation test results and implications. Blood and (or) tumour are sent to a reference laboratory with published high sensitivity for *RB1* testing (see "Genetic Analysis" chapter). Multidisciplinary centres interpret the results and direct the management of the child based on the results. Family members who carry the germline mutation, or whose risk of developing Rb is not clarified by genetic testing, are examined for Rb or retinoma.

Research

Research and academics are major activities of some Rb centres. The capacity for participation in multicentre

clinical trials and initiation of local Rb research in a variety of disciplines are important for training Canada's future Rb specialists, allied health professionals and basic scientists in all fields of relevant expertise, and at various levels (i.e., nurses, social workers, medical students, residents, clinical fellows, graduate students, and postdoctoral fellows).

Classification of Retinoblastoma Centres

Classification of Rb centres is based on the experience within Canada of the components required to optimize care for children with different levels of Rb severity and complexity.

Primary retinoblastoma care

Primary Rb care occurs in the office of a family doctor, pediatrician, optometrist or community-based ophthalmologist, at which the first signs of Rb are recognized and a referral is made to a secondary Rb centre.

Secondary retinoblastoma centre

A secondary Rb centre is a medical teaching hospital that has adequate resources and experience (including equipment and trained personnel) for treatment of unilateral Rb patients and diagnosis and follow-up of more complex cases. Secondary Rb centres are expected to diagnose ≥1 new patient(s) per year. Mandatory and recommended resources for secondary centres are outlined in Figure 1.

Once primary care refers a child with the potential diagnosis of Rb, the secondary Rb centre will establish the diagnosis and develop the initial treatment plan, often in consultation with a tertiary Rb centre.

Secondary centres will refer bilateral Rb cases to tertiary Rb centres, but participate in the care of bilateral cases when the initial treatment plan is developed with the tertiary Rb centre (see "Referral and Diagnosis" chapter). A social worker assigned specifically to Rb families is recommended at secondary centres, especially when the secondary centre will participate in shared management and follow-up of bilateral cases.

Tertiary retinoblastoma centre

A tertiary Rb centre within a teaching hospital has all of the characteristics mandatory in secondary centres, in addition to adequate resources and experience (including equipment and trained personnel) for treatment of bilateral (and rare trilateral) Rb patients (Fig. 1). Tertiary centres typically see ≥3 new Rb patients per year. Rb patients at tertiary Rb centres will be managed by a multidisciplinary Rb team, including ophthalmologists, oncologists, social workers, nurses, imaging and child life specialists. The institution will allocate appropriate resources specifically in support of the multidisciplinary team.

FEATURES AND CLASSIFICATION OF RETINOBLASTOMA CENTRES—RECOMMENDATION

1. We recommend that Rb treatment centres in Canada be classified as secondary and tertiary Rb centres, and be staffed, organized, and equipped according to the criteria outlined in Figure 1 [*Consensus*].

REFERRAL AND DIAGNOSIS

Introduction

These referral guidelines for Canada are intended to encourage immediate referral upon suspicion of retinoblastoma (Rb). Early and immediate referral to the appropriate healthcare professional(s) is essential for timely diagnosis and good treatment outcomes in the care of Rb families. Late referral and delayed diagnosis result in difficult-to-treat large tumours, blindness, extraocular disease, and mortality. Family members of Rb patients are also at risk when genetic testing and counselling are delayed.[52] There is evidence that earlier diagnosis improves treatment outcomes.[13]

The primary care physician plays a critical role in the referral process. Secondary and tertiary Rb centres further establish the diagnosis and develop the initial treatment plan. These guidelines aim to inform clinicians on when, where, and how soon to refer a patient with suspected Rb. While this referral strategy generally already exists in Canada, the process is now formalized in this document as a guideline. Furthermore, these guidelines outline the processes to establish a diagnosis of Rb.

Referral

The primary healthcare practitioner is responsible for making the initial referral with the possibility of a diagnosis of Rb. The primary care practitioner ideally continues with all other standard (i.e., non-Rb) baby or child healthcare and participates in ongoing long-term follow-up.

However, in an interview of parents of 100 Rb patients in the UK, 55% had to consult >1 primary healthcare professional before obtaining a referral to an ophthalmologist, with 19% consulting with >2 primary healthcare professionals.[12] The referral lag (time between the initial visit with a primary healthcare professional and appointment with an ophthalmologist) was a median of 2 weeks (range 1–80), with 49% patients seeing a specialist within 1 week. Even still, about one-quarter (23%) waited >8 weeks (up to over a year for 2/23 patients) before seeing a specialist. This had serious consequences for some patients, although referral lag time did not affect the likelihood of enucleation being used as primary treatment. Patients who required adjuvant therapy to treat spread of tumour outside the globe had a significantly higher referral lag time (median 27 weeks, range 2–61) than those with no evidence of tumour spread (median 8 weeks, range 1–94).

Thus, whenever there is any possibility of Rb, immediate

referral by the primary care practitioner to a secondary or tertiary Rb centre is indicated.[53] This referral is urgent (i.e., within 72 hours or as soon as physically possible). Whether the referral is made to a secondary or tertiary Rb centre may be determined by the specific geographic situation, the expertise required and available, and the severity of the disease. For example, unilateral Rb cases can be referred to either a secondary or tertiary Rb centre, depending on the severity of disease and geographical proximity to the centre. Bilateral and advanced, complicated unilateral cases may be immediately referred to tertiary Rb centres or to secondary Rb centres from which they may subsequently be referred on to tertiary care (Fig. 2).

Diagnosis

Initial diagnosis

The diagnosis of Rb may be suspected by the primary care professional. An urgent referral is indicated, whenever the primary care professional is suspicious of a diagnosis of Rb, on the basis of presentation with signs of leukocoria or strabismus, or a suspicious screening exam (see "Screening" chapter).

Confirmatory diagnosis

Confirmation of the Rb diagnosis at the secondary or tertiary Rb centre requires a retinal examination with full pupillary dilation, the standard of care for a child referred with leukocoria. Confirmatory diagnosis, determination of the extent of the disease, and assignment of IIRC group is accomplished at the examination under anaesthesia (EUA) by a team of experts based on the distinct clinical features of Rb. Other imaging tools can help confirm diagnosis, but unlike other cancers, pathology is not required, since opening the eye to obtain a biopsy would risk tumour spread beyond the eye, endangering the life of the patient. If the affected eye is enucleated, it is then possible to obtain pathologic confirmation of the clinical diagnosis. Obtaining such confirmation is not feasible for non-enucleated eyes.

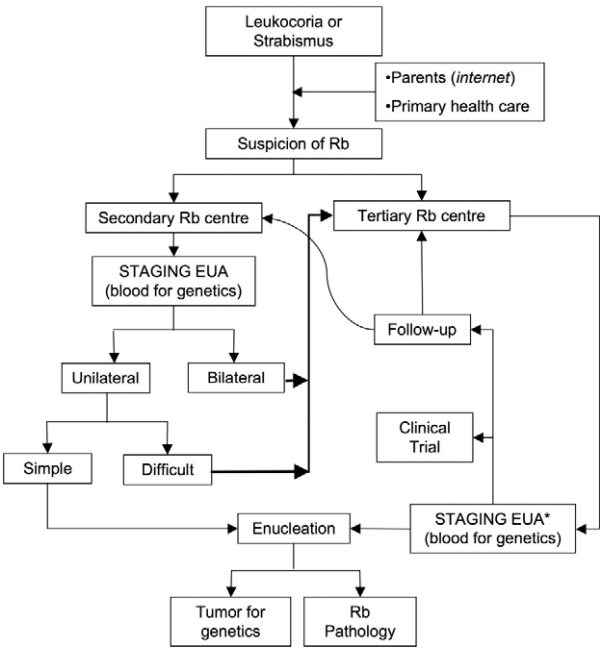

Figure 2– Referral algorithm for retinoblastoma cases in Canada. Rb cases can be referred to secondary or tertiary centres. Secondary centres will only care for simple unilateral cases, and must refer difficult unilateral and bilateral cases to tertiary centres. Tertiary centres can treat both unilateral (not shown) and bilateral cases, and share follow-up care with secondary centres for referred cases.

REFERRAL AND DIAGNOSIS—RECOMMENDATIONS

1. We recommend that any child with signs consistent with Rb be referred to an ophthalmologist or optometrist to receive a full retinal examination with dilated pupil and have a detailed history taken to confirm or rule out a diagnosis of Rb [*Consensus*].
2. We recommend that secondary and tertiary centres accept direct referrals with suspicion of Rb from primary healthcare providers, such as optometrists and family practitioners [*Consensus*].
3. We recommend that primary healthcare providers immediately refer all Rb cases to a secondary or tertiary Rb centre [*Consensus*].
4. We recommend that all children referred with any possibility of Rb be seen within 72 hours, or as soon as possible, at the secondary or tertiary Rb centre for thorough ocular and systemic examination to confirm or rule out a diagnosis of Rb. (If a secondary or tertiary Rb centre is not easily accessible, the patient should be referred immediately first to a pediatric ophthalmologist or retinal specialist or local ophthalmologist or, if they cannot be reached, to an emergency department.) [*Consensus*].
5. We recommend that difficult unilateral cases (e.g., very young child; potential to save the eye; unilateral multifocal and (or) germline *RB1* mutation), or risk for extraocular disease and bilateral cases be referred from a secondary centre to a tertiary centre [*Consensus*].
6. We recommend that any child with high-risk pathological features (see "Follow-up" chapter) be referred to tertiary centre [*Consensus*].
7. We recommend that the Rb centre promptly inform the referring physician of the diagnosis, management, and outcome of the referral, and invite the referring physician to remain involved with the non-Rb care and follow-up of the child, as appropriate [*Consensus*].
8. We recommend that in order to reduce risks associated with radiation exposure, all children with Rb have an MRI of the head and orbits at diagnosis, rather than a CT scan, if possible, to check for evidence of intracranial cancer and the extent of the disease [*Consensus*].

GENETIC ANALYSIS

Introduction

Genetic testing for mutation of the *RB1* gene is key to predicting disease, reducing risks, and monitoring cancer progression. Retinoblastoma (Rb) is considered to be a "genetic" eye cancer, since almost 50% of affected children carry a heritable (germline), predisposing, *RB1* mutation.[52] Ninety percent of the *RB1* germline mutations are **new** in the first affected child (the proband) and were not inherited from the parents. However, each child born to a person with a germline *RB1* mutation has a 50% risk of inheriting the mutation. Although 90% of persons with a germline *RB1* mutation will develop Rb, 10% will develop no tumours and will be unaffected carriers. However, their children will be at risk of developing Rb, even if the parent did not (Fig. 3). Genetic counselling of Rb families is therefore complex, and must rely on accurate interpretation of clinical and molecular data in order to achieve the goal of decreasing the burden of this disorder in both the immediate and extended family.

The role of *RB1* gene mutation in the development of Rb is unambiguous.[54-56] Mutations in both *RB1* alleles are necessary for development of Rb; one mutation may be a germline mutation or a somatic mutation; the second mutation is always somatic, occurring in the retinal cell that progresses to form the tumour. Application of this knowledge to individual families significantly enhances the outcome for children who can be predicted before birth to be affected: their chance of a lifetime of good vision increases; the risk of death from Rb decreases; the intensity and invasiveness of required therapy is reduced; and healthcare costs are lower in the short and long term. Canadian research has contributed significantly to this knowledge base. Canadian Rb families need this science to be used in their care.

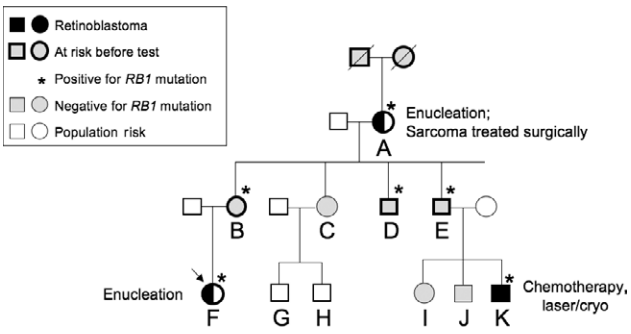

Figure 3–Pedigree with low-penetrance *RB1* mutation. A grandmother (A) with unilateral Rb had no knowledge of her own diagnosis or genetic risk. When her granddaughter, F, was born with unilateral Rb, an *RB1* mutation was identified that was shown to be weak, and only partially inactivated the Rb protein. Three of A's 4 children (B, D, E) were found to carry the same mutation, but showed no sign of Rb or the benign precursor, retinoma. Two grandchildren (I, J) were tested and shown to not have the mutation. Two grandchildren (G, H) did not need testing because their parent (C) was unaffected. The sixth grandchild (K) was diagnosed to be a carrier of the mutation when the mutation was identified in his cousin, F, and was cured of bilateral Rb by chemotherapy and focal therapy. Because the grandmother (A) was aware of the risks for secondary non-Rb cancer, the sarcoma she developed at age 59 was diagnosed early enough for surgery to be effective.

Genetic Testing

Testing the child and extended family members to improve disease management and family planning

Relatives of children affected by Rb (parents, siblings, cousins, and offspring) are also at risk of developing Rb and other cancers. Therefore, it is important to proceed with molecular genetic testing to determine if a heritable *RB1* mutation is present. Once a germline mutation is identified in the proband, at-risk family members can be tested for the precise *RB1* mutation and counselled regarding their risks, and if necessary, early tumour surveillance can be initiated. Depending on the type of *RB1* mutation, 20–100%[57] of persons with germline *RB1* mutations develop Rb, usually in both eyes. For this reason, genetic testing is important for the immediate medical management of Rb; by identifying children at risk prior to detection of tumours, knowledge of the *RB1* mutation supports the requirement for early and aggressive tumour surveillance in order to institute early therapy to optimize outcomes. Failure to identify Rb tumours at the earliest time and smallest possible size compromises visual outcome, and increases the risk of tumours spreading beyond the eye. This is associated with a poorer outcome and requires more aggressive therapy, which is inherently associated with increased risks for the patient.

Prenatal diagnosis enhances early management of Rb-affected infants. Obstetrical ultrasound can visualize large intraocular Rb in the fetus as early as 33 weeks gestation. Even if there are no ultrasound-detectable tumours, there is a 50% risk of visually threatening small posterior Rb by 36 weeks gestation.[54] Therefore, in consultation with obstetrics, medical genetics and pediatrics, premature delivery at 36 weeks' gestation of infants shown to carry a *RB1* mutant allele may be recommended for the earliest possible diagnosis and treatment of Rb.

Determination of the *RB1* status is also important for the healthcare of adult relatives. Persons with *RB1* germline mutations have a greater than usual lifetime risk for other malignancies, including osteosarcoma, sarcoma, melanoma,[58] lung cancer,[59] and other tumours.[60] Radiation therapy greatly increases this risk, especially for brain tumours and sarcomas, particularly when given to children under 1 year of age.[61] Timely identification of adults at risk for secondary non-Rb cancers supports increased patient and healthcare worker awareness to minimize exposure to radiation and achieve early detection and intervention in order to reduce morbidity and mortality (Fig. 5).

In addition to its critical role in the acute care of Rb

families, *RB1* genetic testing underpins genetic counselling and enables informed family-planning decisions. Genetic counselling is key, since accurate knowledge of Rb encourages parental understanding of risk, and supports early diagnosis and optimized health outcomes for children.[62]

Genetic tests focus healthcare resources where they are needed

Children who carry a germline *RB1* mutation are at high risk of developing vision- and life-threatening Rb. The first affected child in a family (the proband) cannot be anticipated, and is usually discovered only when large tumours are present. However, this child is at risk of developing other Rb tumours in the same or other eye. In order to find Rb at the earliest possible age, children at risk (proband and infant relatives) should be routinely examined (either awake or under general anaesthetic) frequently in the first 3 years of life, with depression of the sclera to visualize the entire retina. Rb diagnosed by such surveillance usually requires only focal therapy (laser and cryotherapy) since tumours are detected when they are very small, without the need for more aggressive systemic therapies such as chemotherapy or radiation.

In the absence of knowledge of their *RB1* status, infant relatives receive an extensive series of examinations, many under general anaesthetic, with its inherent risks.[54,56,63] When the *RB1* status of the proband is known, the precise status of each relative can be determined. Since 90% of probands have either new germline mutations or no *RB1* germline mutation, the majority of relatives will be shown to not carry the *RB1* mutation. Offspring of individuals shown to not carry the family's *RB1* mutations have the same risk of developing Rb as anyone else in the general population.

Comparative costs and benefits of genetic testing

A cost-benefit analysis done in 1994 at the Hospital for Sick Children, Toronto, Ontario, Canada, predicted that direct costs savings from avoiding unnecessary examinations substantially exceed the one-time cost of molecular testing for a typical Rb family.[63] In a subsequent study, direct clinical costs were estimated for a randomly selected sample of 20 Ontario Rb families by adjusting Noorani's estimates for inflation. The *RB1* mutations for 18 of the 20 families were identified; mutations for 2 families had not been found at the time of the study. Then, assuming conventional screening for at-risk relatives if genetic analysis is not available (3 clinic exams and 7 examinations under anaesthesia [EUAs] during the first 3 years of life for each relative), genetic testing was shown to save $7000 per family on average.

Actually, net savings are even higher than these conservative analyses,[54,63] for 3 reasons. First, direct costs borne by families (with genetic testing, families make fewer visits to hospital, reducing time off work, travel costs, and family stress) were not evaluated. Second, the analyses also ignore benefits from genetic testing to generations not yet born, who under conventional screening would be considered at risk. Third, significant technological advances continue to be made in molecular analysis that increase test sensitivity and reduce the cost of testing, while clinical wage expenses have increased.

These data strongly support redirecting economic resources to molecular diagnosis in Rb.

Conducting genetic testing

The clinical evidence that a child may or may not have a germline *RB1* mutation is first evaluated. If both eyes are affected, the child almost certainly carries an identifiable *RB1* mutation in the blood. However, for all Rb patients, it is important to preserve the tumour so that high-quality deoxyribonucleic acid (DNA) can be obtained for later study, if blood studies do not reveal an *RB1* mutation. Genetic testing should be conducted in a laboratory certified in clinical molecular genetics with demonstrated sensitivity and turnaround time to identify *RB1* mutations.

Genetic testing for unilateral, nonfamilial retinoblastoma

In individuals with unilateral, nonfamilial Rb, there is only a 15% chance that an *RB1* mutation exists in blood. However, since the sensitivity of *RB1* mutation detection is so high (95%), testing blood from unilateral patients, harvested as early as the first EUA, has a 95% chance of identifying a germline *RB1* mutation if it is there. If no *RB1* mutation is found in the child's blood, further studies are conducted on tumour tissue, when available, with the intent to identify the 2 *RB1* mutations in the tumour. The patient's blood is then screened for the presence of these *RB1* mutations. If no tumour is available, a negative result on blood reduces the chance of a mutation from 15% to less than 1%. These children are repeatedly examined in the clinic for potential development of retinoblastoma in their normal eye, but do not require examination under anaesthetic. The offspring of such patients also do not require anaesthetics for tumour surveillance, but only clinic visits, since their risk for tumour is very small.

In some cases, an *RB1* mutation that has arisen in the early embryo is present in only a fraction of cells, a phenomenon described as "mosaicism."[64] Therefore, even though the *RB1* mutations of the tumour may not be detectable in blood, patients with unilateral Rb still require ongoing tumour surveillance for the normal eye, because they could be mosaic for an unidentified germline mutation.[64] However, the risk is small enough that these examinations can be conducted less frequently and awake, and without anaesthetic.[65]

Therefore, as long as the laboratory has demonstrated that 90% of *RB1* mutations can be identified, a negative result means risks are low enough that EUAs can be avoided. Since mosaicism cannot be inherited, all antecedent relatives are cleared of risk, and future offspring of the proband can be tested to determine if they have inherited the same *RB1* mutant allele tumour as their parent's tumour. For

85% of unilateral, nonfamilial Rb, absence in the blood of the *RB1* mutations identified in the tumour of the proband clears all relatives of the need for molecular testing, except for future offspring (Figs. 4 and 5, Table 6). The 15% of unilateral, nonfamilial patients who are found to carry an *RB1* mutant allele require the same surveillance and management as bilateral, germline cases.

Rb tumour or DNA may be unavailable in an adequate form from a unilateral, nonfamilial Rb proband for many reasons. For example, the eye may have been removed many years ago and not preserved for DNA studies. Alternatively, the affected eye may not have been surgically removed, so there is no tumour specimen available.

Ideally, DNA should be extracted from fresh tumour, or the tumour should be flash frozen to enable sufficient good-quality DNA to be extracted later. DNA isolated from tumour tissue fixed in formalin and embedded in paraffin is fragmented and is suboptimal for analysis. When *RB1* testing is performed in a laboratory with documented high sensitivity to find *RB1* mutations, testing blood without tumour is also useful. Finding a mutation moves the proband into the category of germline Rb. Not finding a mutation reduces the risk that one exists from 15% (pretest risk) to 1.5% if the laboratory sensitivity to find any *RB1* mutation is 90%.

Genetic testing for bilateral and unilateral familial retinoblastoma

Most bilateral cases of Rb are considered to carry a heterozygous *RB1* germline mutation, since it is unlikely for 2 rare somatic mutations to occur in multiple fetal retinal cells.[55,66,67] Therefore, initial molecular genetic testing is performed on peripheral blood DNA in bilateral, unilateral familial and unilateral multifocal (indicative of germline mutation) cases. If no mutation is found in the blood, molecular studies of tumour, if available, may reveal 2 mutant *RB1* alleles that can be tested for in DNA extracted from peripheral blood, as described above. However, tumour may be unavailable if treatment did not include removal of either eye. Since the present state of knowledge indicates that all persons with bilateral or familial Rb carry a predisposing *RB1* mutant allele, failure to find an *RB1* mutation in blood suggests mosaicism, as described above.[65]

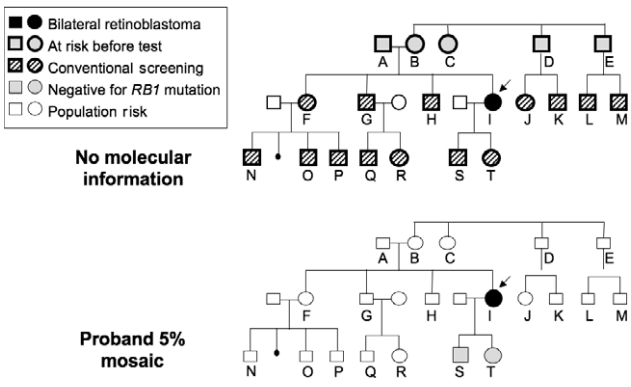

Figure 4 –Comparison of screening with and without knowledge of *RB1* gene status. Individual I (proband, arrow) developed bilateral Rb in infancy. The pedigree shows numerous persons at risk (F, G, H, J, K, L, M, N, O, P, Q, R, S, T). Seven infants underwent surveillance 43 clinic visits and 51 EUAs. Adults received counselling for risk of further cancers (A, B, C, D, E). Blood DNA and RNA studies in 3 different laboratories found no *RB1* mutation and no tumour was available. However, by high-sensitivity allele-specific PCR, the proband was shown to be 5% mosaic for a null *RB1* mutant allele. Because mosaicism cannot be inherited, no antecedent relatives required testing. Two offspring (S, T) tested negative. No further clinical surveillance was required. The risk for secondary non-Rb cancer in the mosaic proband is (presumably) reduced.

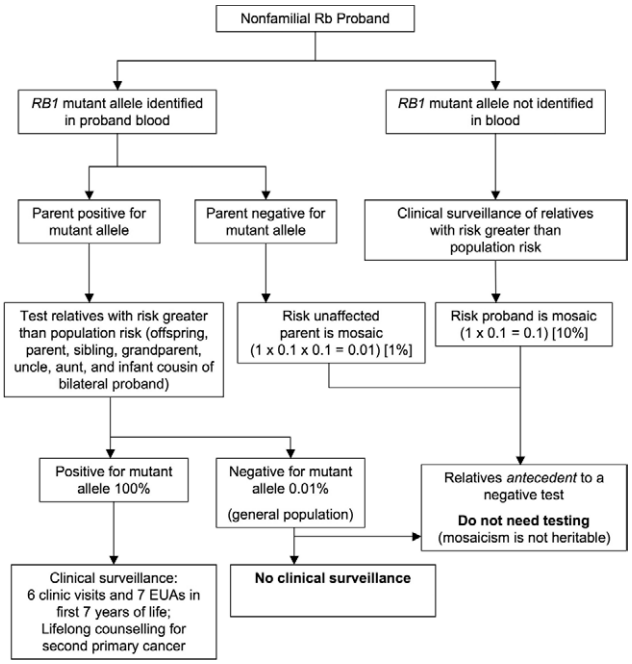

Figure 5–Molecular testing identifies relatives who carry the mutant *RB1* allele of the proband and are at risk for Rb

Table 6. Pretest risk for relatives to carry the mutant *RB1* allele of the proband

	Pretest risk for mutant allele	
Relative of proband	Bilateral proband (1) 100%	Unilateral proband (.015) 15%
Offspring (infant)	(1 x 0.5 = 0.5) 50%	(0.15 x 0.5 = 0.075) 7.5%
Parent	(0.1 x 1 = 0.1) 10%	(0.1 x 0.15 = 0.015) 1.5%
Sibling infant	(0.1 x 0.5 = 0.05) 5%	(0.015 x 0.5 = 0.0075) 0.75%
Sibling adult	(0.1 x 0.1 x 0.5 = 0.005) 0.5%	(0.015 x 0.1 x 0.5 = 0.00075) 0.075%
Grandparent	(0.1 x 0.1 = 0.01) 1%	(0.015 x 0.1 = 0.0015) 0.15%
Aunt/Uncle (adult)	(0.01 x 0.1 x 0.5 = 0.0005) 0.05%	(0.0015x 0.1 x 0.5 = 0.000075) 0.0075%
Cousin (infant)	(0.01 x 0.1 x 0.5 x 0.5 = 0.00025) 0.025%	(0.0015 x 0.1 x 0.5 x 0.5 = 0.000038) 0.0038%
Cousin (adult)	(0.01 x 0.1 x 0.5 x 0.5 x 0.1 = 0.000025) 0.0025%	(0.0015 x 0.1 x 0.5 x 0.5 x 0.1 = 0.0000038) 0.00038%
General population	0.00006667 (1/15,000 live births) 0.006667%	

Genetic Testing Tools

RB1 mutation analysis must be performed for each family, since the majority of mutations are unique. Mutations are distributed throughout the *RB1* gene, with no recognized domains more commonly affected.[54-56] High-quality DNA is i) studied to detect rearrangements, deletions and insertions (quantitative multiplex polymerase chain reaction [PCR]; 25% of all detected *RB1* mutations), ii) evaluated for a set of recurrent mutations by allele-specific PCR (20% of all detected *RB1* mutations), and iii) each exon and flanking intron is sequenced (50% of all detected *RB1* mutations). If no mutation is found, a new blood sample is requested for study of ribonucleic acid (RNA) by reverse transcriptase polymerase chain reaction (RT-PCR). This multi-step approach can currently yield 95% of the *RB1* mutations in a laboratory focusing on *RB1*. Although the cost of individual proband mutation identification for *RB1* is high compared with simple gene testing for other common inherited disorders, its value is clear.

When initial molecular studies fail to identify the causative *RB1* mutation(s), cytogenetic analysis such as karyotyping or fluorescent *in situ* hybridization (FISH) is recommended. Reciprocal translocations that interrupt the *RB1* gene are generally missed by molecular assays, but will be detected using cytogenetic methods. Children with syndromic features associated with large chromosome 13 deletions including *RB1* and undefined adjacent genes[68,69] will frequently be identified by karyotype and (or) FISH before they are recognized to have Rb. Any genetic testing report suggesting that chromosome 13q14 could be deleted or rearranged in a child or adult should trigger an urgent referral of other family members/siblings to an ophthalmologist. Chromosome deletions and rearrangements may significantly impact the risk that another child in the family will be affected.[70,71]

With current technology, a mutation cannot be identified in 5% of Rb families. It is important to retain the clinical samples from these persons for future studies whenever new technology becomes available (Fig. 4).

Determining Who Should Be Tested

Best practice acute care and long-term follow-up of a patient with Rb and his/her family are achieved when there is knowledge of the *RB1* mutant allele of the proband and at-risk relatives. The *RB1* mutant allele can be identified by high-sensitivity molecular testing on blood, facilitated by studies of the Rb tumour, if available. This knowledge is a prerequisite for testing of relatives in order to apply cost-effective clinical surveillance to detect cancer in child and adult relatives who also carry the *RB1* mutant allele and discontinue surveillance in those relatives who are not at risk.

When the RB1 *mutation of the proband is unknown*

Without knowledge of the *RB1* mutation of the proband, all relatives who have a risk of carrying the mutant allele greater than the normal population (1/15,000 [0.001%]) require clinical surveillance for early diagnosis of Rb (infants and children to age 7, including under EUA)[67] and for lifetime risk of secondary non-Rb cancers (all ages).[60] Included in the surveillance are all offspring, parents, siblings, grandparents and, when the proband is bilaterally affected, aunts, uncles, and first cousins (Fig. 4, Table 6).

Testing therefore starts with the proband, then indicated members of the immediate family, followed by parents and siblings of all family members identified as carriers of the proband's germline *RB1* mutation.

In cases of a germline RB1 *mutation*

The offspring of a parent with a germline *RB1* mutation have a 50% chance of inheriting the *RB1* mutant allele. Testing can be done to assist in family planning decisions and at any stage of pregnancy to optimize the outcome for infants carrying the *RB1* mutant allele. If appropriate, infants with the *RB1* mutation can be safely delivered 4 weeks prematurely (36 weeks' gestation) for early management of vision-threatening tumours. For such cases, the pregnancy should not be allowed to progress beyond the due date.

Parents of the proband will be tested for the *RB1* mutant allele in order to establish the risk for their other children; their own personal risk for other cancers;[60] and the risk to antecedent relatives and their offspring. For each relative found to be positive for the *RB1* mutant allele, the next immediate relatives (parents and siblings) must be tested. When an antecedent relative tests negative for the proband's mutation, no further antecedent relatives need be tested, since mosaicism is the only circumstance that can lead to a "false negative" result and cannot be inherited (Fig. 4). However, the children of the first antecedent person who tests negative for the mutation need testing in case of undetectable mosaicism in their parent.

Cases with reduced-penetrance RB1 *alleles*

Although the most common type of *RB1* mutant allele is "null" (no detectable Rb protein), some uncommon types of alleles result in Rb protein that is partially functional or present at low levels. These reduced-penetrance *RB1* alleles result in fewer Rb tumours, more unilateral disease and more unaffected carriers of the *RB1* mutant allele. The identification of reduced-penetrance *RB1* alleles is particularly important, since unaffected blood relatives may assume they do not carry the predisposing *RB1* mutant allele of the proband, putting their own children at risk of suboptimal outcomes due to delayed diagnosis.

Harvesting and Analyzing the Tumour

Blood and (or) fresh or frozen tumour tissue or DNA samples are sent to a qualified molecular diagnostic laboratory to be analyzed. The optic nerve is separated from the eye that has been surgically removed and placed in a separate formalin container. The eye is immediately opened in order to obtain fresh tumour for DNA. Care is taken to avoid disturbing the tumour-optic nerve and tumour-choroid relationship, or areas noted clinically to be important

for pathological examination. The Rb tumour is placed in tissue culture media for rapid transport to the testing lab, or frozen at –60° C for future testing and tumour banking. Inadequate Rb tumour collection reduces the accuracy of molecular diagnosis for unilateral Rb patients. Thus, it is important that tumour and blood samples are drawn properly and delivered to a laboratory focusing on *RB1* mutation clinical work. This is the best way to determine if the child with unilateral nonfamilial Rb has a germline *RB1* mutation. Rb tumour is also useful for bilaterally affected or familial Rb if blood studies fail to identify an *RB1* mutation.

Genetic Counselling

Purpose of genetic counselling

The purpose of genetic counselling is to educate probands, parents, and relatives about the heritability of Rb and future health risks to affected individuals, and to discuss the risks of developing Rb, screening protocols, general information regarding Rb risks for future children to be affected, and reproductive options.

Initial consultation

An initial consultation with the family in a genetics clinic will provide a basic overview of Rb genetics, including basic genetic facts. A family history will be obtained and a detailed pedigree drawn, identifying relatives at risk. Further discussion will explain the details of genetics, purposes of testing and likely outcomes, test sensitivity and residual risks. Genetic testing is offered, and if the family is agreeable, informed consent to test is obtained. If possible, informed consent to use the genetic information for the benefit of related individuals at risk will also be obtained. Once this paperwork is completed, preparations are made for genetic testing, alerting the laboratory and collecting and delivering specimens. Since the technology to find the *RB1* mutations in proband samples is highly specialized and most effectively performed on more than 100 samples per year, several specialized laboratories around the world offer this test. It is important that the sensitivity (% of all tested samples in which the mutation(s) are found, resulting in a useful report) and turnaround time of each laboratory are documented with evidence.

A second counselling session is arranged to report and interpret the results. Once the results are reported, the family is asked to contact the relatives at risk so that they can be referred for counselling and testing. This information is documented with a letter placed in the proband's chart and given to the family. The family's primary care physician also receives a copy of the report. Once the results have been reported to and interpreted for the family, the genetic counselling differs for each family based on the genetic result.

Counselling when a germline mutation is detected in the proband

The family will be made aware that presymptomatic and prenatal diagnosis is possible for any relative at risk. Early prenatal counselling and molecular testing are important to allow for informed family-planning decisions and critical perinatal management of affected babies. When the specific *RB1* mutation is known, any at-risk pregnancy can be tested by chorionic villi biopsy (before 12 weeks' gestation) or amniocentesis (at any stage of gestation). Risk of miscarriage is reported to be between 0.13 and 1.9%[72–75] of pregnancies undergoing amniocentesis during the second trimester. Pre-implantation genetic diagnosis is feasible. However, there is some statistically significant increased risk of retinoblastoma to develop in children conceived after in vitro fertilization.[76,77] Commonly, parents of children at 50% risk chose amniocentesis at 32 weeks' gestation in order to have the option of delivery 2 weeks prematurely at 36 weeks' gestation, when there is a 50% risk of a paramacular tumour already being present. Alternately, cord blood can be tested for the *RB1* mutation identified in a relative, followed by intense surveillance for tumours for those children who carry the *RB1* mutation.

If the baby is shown to carry the *RB1* mutation of their parent, there is a 50% chance that an Rb tumour will be present at birth. Obstetrical ultrasound of the eyes can detect medium-sized tumours and is advised to begin at 32 weeks' gestation. Even if the ultrasound is normal, early delivery at 36 weeks' gestation is advised to catch tiny tumours when they can be treated with only laser and cryotherapy, as appropriate.

We recommend that *RB1* mutation carriers be monitored for new tumours with frequent EUAs or clinic visits until 9 years of age (see "Follow-up" chapter). Lifelong counselling for increased risk of other tumours[60,78] is important (see "Follow-up" chapter). Relatives proven not to have the family's *RB1* mutation do not require further clinical surveillance.[62]

Counselling when neither tumour RB1 *mutation is detected in blood*

When neither of the *RB1* mutations discovered in the proband's tumour is found in his or her blood, the individual may have no mutation or be mosaic for the *RB1* mutation in a low fraction of cells that it is not detected by the laboratory test. However, since mosaicism cannot be inherited, parents and siblings are not at risk. Offspring of the proband are at low risk and should be tested for the *RB1* mutant alleles found in the Rb tumour at any stage of pregnancy or immediately after birth. During genetic counselling, the proband and his/her family will be informed of the small remaining risk for the unaffected eye to develop tumours (and the potential low risk for other types of tumours). Monitoring of the other eye is still required, usually without general anaesthetic. As with counselling when germline mutations are found, prenatal and presymptomatic diagnosis is suggested for the children and future children of Rb probands with tumour mutations not detected in blood.

Counselling when no RB1 *mutation is found in blood of unilateral probands with no available tumour*

When the sensitivity of the test used to identify an *RB1* mutation, if it is present, is above 90%, absence of a detectable mutation in blood reduces the risk that a mutation exists from 15% to 1.5%. This is very important for families, since it reduces risk for offspring of the unilateral unaffected *adult* to 0.075% (0.1 x 0.75) (Table 6), which is approaching the risk for the general population to develop Rb. Therefore, the children of unilateral parents with no identifiable *RB1* mutation in blood can be spared EUAs, and they can be checked in the clinic less frequently. This benefit to healthcare for the family is only valid if the laboratory test sensitivity to detect new *RB1* mutations is known.

Counselling when the mutation is unknown

If no testing is done or no mutation is found in blood of a person with bilateral Rb, and the tumour is not available for analysis, clinical examinations and family counselling for all relatives at risk (Table 6) follow conventional strategies. It is important to maintain contact with the proband, since new tests and knowledge may eventually identify the mutation.

Dissemination of test results

It is recommended that all genetic test results and information discussed at each counselling session be recorded in the proband's medical record. It is important for future care that copies of these letters be retained by the family and the proband, so that they can fully inform their healthcare professionals.

Long-term follow-up

Long-term follow-up and regular counselling for long-term risks associated with the *RB1* gene mutations are important and are discussed in the "Follow-up" chapter. It is especially important to counsel affected teenagers who are becoming sexually active; they need to understand the biology and genetics of Rb and the *RB1* gene, particularly of their own mutant allele and its potential effect on their future children.

GENETIC ANALYSIS—RECOMMENDATIONS

Genetic testing

1. We recommend *RB1* gene mutation identification testing for the first affected person (proband) in each Rb family [*Level 2*].[54,56]
2. We recommend that any tumour removed from a Rb patient be stored in a form appropriate for DNA studies. [*Level 2*].[54,56]
3. For bilaterally affected and familial unilateral probands, we recommend that blood be studied, aided by tumour tissue as required [*Level 2*].[54,56]
4. For unilateral, nonfamilial probands, we recommend that tumour be studied first. If no tumour is available, we recommend that blood be studied [*Level 2*].[54,56]

When chromosome 13q14 deletion is discovered

5. We recommend that any genetic test report suggesting deletion or rearrangement of chromosome 13q14 in a child or adult trigger an urgent referral to ophthalmology within 48–72 hours [*Level 2*].[68,69]

When the family RB1 *mutation is known*

6. We recommend genetic testing for all at-risk relatives [*Level 2*].[54,56]
7. We recommend frequent clinical surveillance to detect Rb in children who carry the *RB1* mutant allele of their family [*Level 2*].[54,56]
8. We recommend awareness counselling about cancer in adult relatives who carry the *RB1* mutant allele of their family [*Level 2*].[60,79,80]
9. We recommend that surveillance for relatives not at risk be discontinued (Fig. 4) [*Level 2*].[60,79,80]
10. We recommend early prenatal counselling, including a discussion of the advantages and disadvantages of invasive prenatal testing to support informed family-planning decisions, and perinatal management of affected babies to facilitate the earliest possible treatment of tumours (Fig. 3) [*Level 2*].[54,80]

When the family RB1 *mutation is not known*

11. With a positive family history but no knowledge of the *RB1* mutation, we recommend that each at-risk family member be screened until age 7 years, according to the empiric risk of developing Rb (Figs. 3 and 4) [*Level 2*].[54,67,80]

Genetic counselling

12. We recommend genetic counselling for patients, parents and other relatives to discuss Rb, the risk and hereditary pattern of Rb, pregnancy options, postdelivery screening protocols and treatment options [*Level 3*].[55,67]
13. We recommend genetic counselling to explain the benefits and process of molecular analysis of the proband's *RB1* genes [*Level 3*].[55,67]
14. We recommend that the details and impact of the *RB1* mutant allele be explained to the affected children and the family soon after the testing is complete. The clinical geneticist can counsel on the risks and therefore the intensity of recommended surveillance of children at risk to develop Rb [*Level 3*].[55,67]
15. We recommend that children with *RB1* mutant alleles be offered repeated genetic counselling as they grow up, so that they completely understand their options and appropriate care [*Consensus*].

TREATMENT

Introduction

Retinoblastoma (Rb), the most common eye cancer in children (1 in 15,000 live births), is fatal if untreated. With timely detection and care by multidisciplinary teams using current technology and treatment protocols, >95% of patients can be successfully treated before the cancer spreads outside of the eye.[47,52]

Survival of the child is the overriding goal of treatment. Retaining the affected eye, preserving vision, and producing good cosmetic results are also important. However, therapy to achieve these goals must never jeopardize the child's chance of cure.

A systematic approach in the context of formal collaborative clinical trials has resulted in excellent outcomes for childhood cancer in general. Children with Rb should similarly benefit by the systematic implementation of guidelines and clinical trials that can be audited for effectiveness and toxicity. However, there are no published Rb multidisciplinary treatment clinical trials and, consequently, little evidence-based therapy.[8] Due in part to the challenge of accruing enough research subjects, and design difficulties related to 2 eyes treated both individually and systemically, organized formal clinical trials in Rb have not yet succeeded, worldwide.[9,52] This chapter will give an overview of the current Rb treatment warranted for different stages and scenarios of disease, and conclude with recommendations for a standardized treatment plan for Canada.

Classification

Classification of disease severity is critical to determine which therapy is most appropriate for a particular eye and child, and to predict treatment outcome.[45] In 1958, the Reese-Ellsworth (R-E) classification was devised to predict the outcome of eyes treated with external beam radiotherapy (EBR).[81] Since the long-term complications of radiation for children with *RB1* constitutional mutations include a high lifelong risk of secondary non-Rb cancers with poor survival rates, chemotherapy and focal therapy have replaced EBR as primary treatment worldwide.[47,82-84]

The International Intraocular Retinoblastoma Classification (IIRC) was developed for prognosis staging of eyes with intraocular Rb treated with chemotherapy and (or) focal therapy (Table 7).[45]

Cancer is staged for overall prognosis using the American Joint Committee on Cancer/International Union Against Cancer Tumor, Node, Metastasis (TNM) staging system.[85,86] The TNM classification for Rb has been revised[87] to be consistent with the IIRC for intraocular disease (T1–T4a) while staging extraocular disease (T4b, c, d) additionally for lymph node involvement (N1) and metastasis (M1 for distant bone marrow and other metastases) and pathology (pTNM) (see "Follow-Up" chapter).

Ophthalmology Treatments

Classification and staging of severity of disease require examination under anaesthesia (EUA), with appropriate imaging under the same anaesthetic (indirect ophthalmoscopy, RetCam™, B-scan 2D ultrasound, ultrasound biomicroscopy [UBM], fluorescein angiography). If the optic nerve is not visible, computerized tomography (CT) or magnetic resonance imaging (MRI) of the head and orbit is performed prior to the EUA. While CT is easy and quick in most centres and shows the pathognomonic calcification of Rb, it does incur radiation exposure that may increase risk of second primary tumours in individuals with germline *RB1* mutation.[88] MRI is preferable for these cases, since it entails no radiation exposure. Either MRI or CT is important to rule out the very rare pineal/suprasellar trilateral Rb. However, MRI has additional advantages in imaging for suspicious involvement of the optic nerves, and meningeal disease of the brain and spinal cord. In some centres and for specific indications, whole-body MRI may be used for surveillance of metastatic disease[89,90] potentially replacing the nuclear medicine bone scan.

Blood for genetic testing is usually drawn at first EUA (see "Genetic Analysis" chapter). Lumbar puncture and (or) bone marrow should be considered when IIRC Group E eyes show signs that indicate risk of extraocular disease, such as periorbital cellulitis or proptosis.

When the workup is complete, treatment planning is based on the intraocular (IIRC) and systemic tumour classification (TNM) (extent of disease), the potential for cure, with control of intraocular tumours in the long term and useful vision for each eye, balanced against the morbidity of the proposed treatment. Every aspect of risk-benefit of the proposed treatment plan is examined, and the final decisions are made in team discussions that include the parents.[45,91] The first priority is cure to save the child's life, second to save the eye(s), and finally to optimize visual function for patients with either unilateral or bilateral Rb.

Enucleation

When Rb is confined within the eye, enucleation is an excellent way to cure the disease.[45,84,92] For unilateral, unifocal Rb, enucleation is the safest treatment, recommended

Table 7. International Intraocular Rb Classification (IIRC)[45]

Group A: Very low risk **Small discrete tumours not threatening vision (T1a)**
• All tumours are 3 mm or smaller, confined to the retina • Located at least 3 mm from the foveola and 1.5 mm from the optic nerve • No vitreous or subretinal seeding
Group B: Low risk **No vitreous or subretinal seeding (T1b)**
• Tumours any size or location not in Group A • No vitreous or subretinal seeding • Subretinal fluid no more than 5 mm from tumour base
Group C: Moderate risk (T2) **Focal vitreous or subretinal seeding and discrete retinal tumours of any size and location**
• Local, fine, and limited seeding (T3) • Discrete intraretinal tumours of any size and location (T2b) • Up to one quadrant of subretinal fluid (T2a)
Group D: High risk **Diffuse vitreous or subretinal seeding (T3b)**
• Diffuse intraocular disseminated disease • Extensive or "greasy" vitreous seeding • Subretinal seeding may be plaque-like • More than one quadrant retinal detachment
Group E: Very high risk (T4a) **Very high risk with one or more of the following:**
• Irreversible neovascular glaucoma • Massive intraocular hemorrhage • Aseptic orbital cellulitis • Tumour anterior to anterior vitreous face • Tumour touching the lens • Diffuse infiltrating Rb • Phthisis or prephthisis

for IIRC Group D and E eyes. Combination chemotherapy and focal therapy now have good success for Group B and C eyes, but if there is not a good response, the best interests of the whole child, rather than the eye, will be the basis for ongoing treatments. Group E eyes are a significant risk to life, are generally unsalvageable and therefore are enucleated as primary treatment, whether the disease is unilateral or bilateral. Even the best of current therapies usually fail to save such eyes, yet incur significant morbidity and risk extraocular and metastatic extension.[84] When these circumstances are clearly explained to parents, they generally agree with what is in the child's best interests. If there is disagreement of parents with the medical advice for enucleation, careful discussion usually reaches compliance with life-saving therapy. In Canada, a court order can be sought if necessary, and in the only known case, it was actually a relief to the parents when the decision was taken for them.

For both unilateral and bilateral disease, even if chemotherapy is required in the better eye, a test-trial of chemotherapy for a Group E eye may be very dangerous. The pre-enucleation chemotherapy may mask the high-risk pathological features predicting extraocular spread, and even mask existing extension outside the eye. The systemic disease staging would then be wrong, and undertreatment of systemic disease can be fatal.[93]

In planning the management of bilateral Rb, vision status of both eyes, treatment morbidity and staging are all considered. For example, enucleation is indicated for a Group D eye when the other eye is a Group A, which can be cured with focal therapy alone. In exceptional circumstances, removal of both eyes upfront as the first treatment (bilateral primary enucleation) may be the recommended management in the best interest for the child's survival; this might be required to avoid the risk of systemic metastasis if both eyes present with severe Group E disease. It is unusual to cure such severely compromised and dangerous Group E eyes, which have extremely poor visual potential. Therefore, it may also not be in the best interest of the child to be exposed to the chemotherapy or radiation-related morbidities with little possibility of a good outcome.

Enucleation may also be performed for recurrent tumours when all other treatment modalities have failed, or for complications such as total retinal detachment, complete media (vitreous) opacity and total hyphema (blood filling the eye) that prevent evaluation and treatment of potentially progressive tumour.

During enucleation of the eye with Rb, the utmost caution is taken to avoid inadvertent perforation of the eye, or cutting across tumour in the optic nerve. A long (8–12 mm) optic nerve will be excised with the eye.[52] To facilitate molecular diagnosis, the enucleated eye is opened immediately after removal in order to harvest a fresh tumour sample for *RB1* gene studies before formalin fixation for pathology (see "Genetic Analysis" chapter). In the acute care of the child and family,[62] determination of the 2 *RB1* alleles in the tumour are important to establish if the child has a constitutional mutation incurring risk for tumours in the remaining normal eye and for secondary non-Rb cancer. The unique DNA sequence of the mutant alleles may also be useful in surveillance for metastasis and monitoring response to treatment.[94]

A spherical implant is inserted to replace orbital volume, to which muscles are attached to facilitate movement of the final prosthetic eye. A temporary prosthetic eye can be inserted immediately instead of the conventional, clear conformer, and is psychologically beneficial for the families and children,[95] since the child will look "normal" and not need an eye patch after the first 48 hours post-enucleation. An ocularist can later fit the child for a proper prosthetic eye, preferably as soon as postoperative inflammation subsides (usually in about 4–6 weeks).

Delayed enucleation may put the child at risk for extraocular Rb and life-threatening metastatic disease. Complications of enucleation are uncommon, but may include infection, orbital implant extrusion (which requires repair) and ptosis (drooping of the eyelid).[96,97]

Pathology of enucleated eye

The enucleated eye is studied histopathologically to confirm the clinical diagnosis of Rb and particularly look for signs the tumour might have escaped. Diagnostic features of Rb include the characteristic Flexner-Wintersteiner rosettes (photoreceptor-like cells in a single cell spheroid with hyaluronic acid in the lumen), Homer Wright rosettes (photoreceptor-like cells in a single cell spheroid with nerve processes in the central lumen; typical of many neural tumours), undifferentiated cells with little cytoplasm, nuclear moulding of tightly packed cells, pseudorosettes (reflecting collars of live cells extended only about 20 cells from blood vessels, surrounded by dead cells due to hypoxic necrosis), and numerous mitotic and necrotic cells. Rb tumour cells stain strongly for markers of proliferation such as Ki67/MIB-1. Many eyes enucleated for Rb also contain the benign precursor, retinoma, which manifests as nonproliferative (Ki67-negative), benign-appearing cells interspersed with fleurettes (linear stretches of photoreceptor-like dysplasia with bulb-like outer segments that look like fleur-de-lys).[98]

Management of the child is critically dependent on rigorous assessment of the tumour-optic nerve and tumour-choroid-sclera relationships. Tumour extension past the lamina cribrosa of the optic nerve head indicates increased risk that tumour has spread into the meningeal space and cerebrospinal fluid (CSF). Tumour extension into the choroid, sclera, the anterior chamber, iris, or ciliary body indicates increased risk for tumour metastasis, particularly to bone marrow and bone.

Focal Therapy

Focal therapy with laser or cryotherapy physically destroys both dividing and nondividing tumour cells and surrounding tissues. It is effective in destroying small Rb tumours (for example, in Group A eyes) and residual intraocular tumour

after chemotherapy, which kills only dividing tumour cells. Focal therapy is best given repeatedly at regular intervals (3–4 weeks), at reasonable intensity, to avoid eye complications.[99] Any definitive tumour, or suspicious translucent, elevated mass with blood vessels, or tumour extending beyond the documented margins of scars, is retreated until all tumours become inactive, flat, pigmented chorioretinal scars.[100] Fluorescein angiography is helpful to visualize tumour blood vessels as the first sign of recurrence, when focal therapy can eradicate the tumour.

Cryotherapy

A trans-scleral cryoprobe cooled by nitrous oxide is used to double or triple freeze-thaw and destroy the tumour and underlying choroid. Ice crystals lyse the tumour cell membranes.[101] Cryotherapy is primarily used to treat small peripheral Rb, and for peripheral recurrences after chemotherapy.[99] The tumour is directly visualized by indirect ophthalmoscopy or RetCam™, while indenting the sclera under the tumour with the cryoprobe. To avoid complications, no more than 4 different sites are frozen in no more than 2 quadrants of the eye in each session. Freezing calcifications should be avoided, since retinal holes may result.

Before cryotherapy for tumours in the superior retina, a laser barrier line may be placed posteriorly to limit serious effusion and retinal detachment. Posterior tumours that are resistant to laser may be treated with cryotherapy by placing the cryoprobe posteriorly through a small incision into the Tenon space (a procedure termed "cutting cryo").[52]

As demonstrated in animal studies, cryotherapy can be applied before chemotherapy to increase penetration of chemotherapy drugs given within 48 hours of the cryotherapy into the vitreous.[46] Such cryotherapy is indicated for eyes without retinal detachment, less than 72 hours before systemic chemotherapy for IIRC Group D tumours, vitreous seeds, and recurrences. The technique consists of a single freeze application to an area of healthy peripheral retina in the vicinity of the vitreous seeds, or adjacent to the tumour mass.

Laser therapy

Laser coagulation is used for small tumours, residual tumour after chemotherapy, and recurrences after chemotherapy, particularly for lesions posterior to the equator.[102] Laser coagulation acts by physically destroying viable tissue and tumour with heat. Green wavelengths (532-nm/argon, or 536-nm) heat well when in proximity to underlying pigmented tissue, but penetrate white tumours poorly. Infrared (810-nm diode) or far infrared (1064-nm 1 second continuous-wave Nd:YAG) laser can penetrate more deeply with less dependency on pigmentation.[62]

Ideally, laser therapy results in a flat scleral scar with pigmentation, or a flat residual white, gliotic (scar-like) appearance devoid of tumour vessels, both of which indicate a complete response. Complications of laser therapy include failure to control tumours and consequences of overtreatment. Retreatment of gliosis (a scar) can escalate scarring with potential vitreoretinal traction. Peripheral retinal ischemia may result from many repeated laser treatments, which may isolate a portion of retina, and lead to neovascularization. Fluorescein angiography is useful to differentiate active tumour from gliosis or neovascularization.[62] Gliosis requires no treatment, while retinal neovascularization requires laser to the hypoxic retina to decrease the neovascular stimulus.

The 810-nm diode laser in particular may produce scars that extend over time[103,104] and compromise vision, especially if close to the fovea. Excessive laser energy can cause hemorrhages, tumour disruption, holes in the inner limiting membrane, retinal traction and (or) vitreous seeding. Finally, lasering through an inadequately dilated pupil can cause iris burns, pupil deformities, or cataracts.[62]

Chemotherapy

Local chemotherapy

Local carboplatin chemotherapy (subconjunctival or sub-Tenon membrane) has been used alone, or as an adjunct to systemic chemotherapy, to increase the intravitreal carboplatin concentration.[105,106] Complications include acute swelling and morbidity, fibrosis of the periocular tissues causing restricted eye movement, necrosis of the periocular fat and enophthalmos (sunken eye). Fibrosis and adhesions may increase difficulty of subsequent enucleation, with the theoretical risk of rupture of the eye, spilling tumour.[107] Periocular chemotherapy is not used as primary treatment for advanced disease; however, the Children's Oncology Group (COG) has an ongoing clinical trial including local carboplatin (ARET 0231; A single arm trial of systemic and subtenon chemotherapy for groups C and D intraocular retinoblastoma).

Systemic chemotherapy

In the last decade, chemotherapy has largely replaced EBR as the primary treatment for Rb.[5,47,82,108-111] Systemic chemotherapy combined with focal therapy is primarily used to treat bilateral IIRC Group B, C or D eyes and rare unilateral IIRC Group B or C eyes with good vision potential (though chemotherapy is generally not indicated for unilateral disease). Chemotherapy reduces tumour size, and promotes resolution of retinal detachment and regression of vitreous seeds.[47,112] Chemotherapy alone, however, will rarely cure Rb, and requires consolidation of the chemotherapy response by focal therapy (including laser coagulation, cryotherapy and brachytherapy).[5,82,103,113]

Experienced oncologists administer chemotherapy in pediatric oncology units at centres with special expertise in Rb. Most chemotherapy protocols for Rb are based on the combination of carboplatin, etoposide, and vincristine (CEV) in differing doses at 3-week intervals.[47] A significant decrease in size of the tumours is expected with the first few cycles of chemotherapy, with resolution of retinal

detachment in many cases. Focal therapy is administered to definitively eradicate any remaining active tumour after completion of chemotherapy.[62] As shown for the CEV-cyclosporine A (CSA) protocol, additional chemotherapy can successfully rescue a reasonable proportion of affected eyes that cannot be controlled with focal therapy.[47] Eyes that fail chemotherapy and focal therapy have a 50% chance of salvage by radiation therapy or plaque therapy. Eyes failing all other therapies require enucleation to preserve the life of the child, a far more important goal than preserving vision.

Neo-adjuvant chemotherapy and focal therapy for intraocular retinoblastoma

Systemic chemotherapy is generally *not* indicated for unilateral IIRC Group C, D or E eyes, or in bilateral Rb cases where the other eye is IIRC Group A with good visual potential. Enucleation is the preferred option for unilateral Rb, since most unilaterally involved eyes contain large difficult-to-treat tumours, and have a poor visual potential even if the tumours can be cured. That said, some unilateral IIRC Group B or C eyes with good visual potential may be cured by chemotherapy and focal therapy, avoiding enucleation. However, radiation for unilateral Rb is *not* recommended because of the associated long-term morbidity and secondary non-Rb tumour risk.

Postenucleation adjuvant chemotherapy for high-risk pathological features

When high-risk features such as choroidal, scleral and (or) optic nerve invasion are demonstrated pathologically in the enucleated eyes, prophylactic adjuvant chemotherapy may be used to treat potential metastatic disease. Prophylactic harvesting and cryopreservation of autologous hematopoietic stem cells may be carried out, in case metastatic disease develops in future.

Chemotherapy for extraocular and metastatic retinoblastoma

Patients with extraocular or metastatic disease, at either initial presentation or relapse, may be treated with further chemotherapy. This may include intrathecal chemotherapy and high-dose chemotherapy with autologous stem cell rescue (bone marrow or hematopoietic stem cells). If Rb has spread to the bone marrow, bone or other organs or tissues, treatment may include enucleation of the eye with Rb, systemic chemotherapy, surgical excision of any involved organs and tissues (if possible), and autologous hematopoietic stem cell transplant if there is a good chemotherapy response.

If there is orbital invasion by Rb tumour, tumour extending to the cut end of the optic nerve, tumour involvement of the optic chiasm or tumour invasion of the brain, the eye with Rb is enucleated, followed by systemic chemotherapy, multidose intrathecal chemotherapy for several years through an Ommaya reservoir (e.g., topotecan with cytarabine), irradiation of the involved tissues, and (or) autologous hematopoietic stem cell transplant if there is a chemotherapy response.[114] There is no indication for exenteration of the orbit for Rb, since even massive proptosis will respond to chemotherapy, with more effective palliation than mutilating surgery.

Tumour of the meninges of the brain and spinal cord is not curable today, since chemotherapy does not adequately reach the tumour, and irradiation is too toxic to the brain and spinal cord. Palliative radiation is helpful at the right time for specific pain and paralysis control.

Supportive care during treatment

Systemic chemotherapy for a child with Rb is generally given through a central vascular access line, usually a Port-A-Cath®. The central line must be heparinized every 4 to 6 weeks by specially trained personnel in the oncology clinic or at EUA. The central line will remain for more than 1 year after active tumour has been treated, in case tumour recurs.

Many oncologists advise parents against giving acetaminophen while the child is on chemotherapy in case it masks fever, and delays diagnosis of a developing infection. Parents should take the child to the hospital rather than treat a fever at home. If a patient with a central line develops a fever, blood culture is performed, and if neutropenic, must be admitted for immediate prophylactic intravenous (IV) antibiotic therapy according to institutional guidelines. If the blood culture is positive, the patient may be treated for a full 14-day course of the appropriate IV antibiotic therapy. Patients with central lines also require subacute bacterial endocarditis (SBE) prophylaxis for any dental manipulations or surgery (usually a single large oral dose of amoxicillin 1 hour prior to the dental manipulation).

Vaccines, whether routine or special, are given to children on chemotherapy under the advice of the pediatric oncology team according to approved guidelines. Generally, patients undergoing chemotherapy do not receive routine killed or live-attenuated vaccines unless more than 9 months have passed since completion of chemotherapy. If a child with a negative varicella-zoster (chicken pox) blood antibody titer is exposed to chicken pox or herpes zoster (shingles), or develops a rash suspicious of varicella-zoster, the primary physician needs to be notified and appropriate actions taken (e.g., acyclovir or zoster-immune globulin treatment). Children who have previous documented varicella-zoster or VSV vaccine may develop reactivated chicken pox or shingles while receiving immunosuppressive chemotherapy. Both chicken pox and shingles are treated with the IV or oral antiviral drug acyclovir (Zovirax®).

There is a very small risk of chemotherapy-induced secondary acute myelogenous leukemia and myelodysplastic syndromes from the use of etoposide and carboplatin.[115] Therefore, long-term follow-up is mandatory in order to institute therapy as soon as possible, and to quantify these risks in chemotherapy-treated Rb patients (see "Follow-up" chapter).

Radiotherapy

Worldwide, radiotherapy is now rarely given for primary Rb, due to the high risk of inducing secondary non-Rb

cancers, cosmetic side effects and the fact that excellent results are achievable with chemotherapy/focal combination therapy. Patients with Rb who were previously treated with EBR have an increased risk (up to 50%) to develop secondary non-Rb malignancies.[48,49,58,60,78,80,116-118] This risk is especially high for those treated with EBR prior to 1 year of age, but secondary non-Rb malignancies may occur after radiation given at any age.[61] EBR can cause facial deformities, cataracts, and dry eyes.

Nevertheless, EBR remains a very useful treatment for Rb when chemotherapy/focal therapy has failed to control the tumours. Stereotactic or intensity modulated radiotherapy (IMRT) radiation techniques can result in delivery of a lower radiation dose to normal tissues surrounding the target area, with reduced risk of inducing secondary non-Rb malignancies or cosmetic deformities.[119-121] Orbital EBR may supplement chemotherapy for orbital tumour recurrence following enucleation. Brachytherapy is an excellent treatment for small isolated tumours situated well away from the optic nerve or macula, and (or) when tumour recurs focally following chemotherapy or EBR.

Despite the use of radiotherapy for salvage of eyes in which chemotherapy and focal therapy were unsuccessful, enucleation of the remaining eye may be required to save the child's life.

Clinical Trials

The "gold standard" for pediatric oncology care in North America is to offer voluntary participation in multicentre collaborative clinical trials whenever possible and appropriate for the optimal care of the child. If participation is refused, treatment using the best current evidence-based therapy is recommended. Clinical trials and studies may include multicentre, collaborative therapeutic trials, biology studies, supportive care studies, quality-of-life studies and long-term follow-up studies. For patients who relapse, participation in early, phase I and II clinical trials may be appropriate.

The best evidence-based treatment of every Rb child is also in the context of carefully thought-out, progressive clinical trials. Clinical trials may be available through international consortia, such as the Children's Oncology Group (COG), national groups such as the Canadian C17 Research Network, or individual institutions, such as The Hospital for Sick Children.

TREATMENT—RECOMMENDATIONS

1. We recommend that children with Rb be cared for by a multidisciplinary team that provides coordinated and collaborative care in and shared between specialized centres, where expertise, up-to-date protocols, and modern equipment are available for the optimal management of Rb [*Consensus*].
2. We recommend that tertiary Rb centres work together to assure optimal care for each child. This might include referral of children from one centre to another for consultation or to access specific technical or human resources [*Consensus*].
3. We recommend that enrolment in a formal clinical trial remain the gold standard for improving treatment and care of children with cancer, including Rb [*Consensus*].

Ocular treatments

4. We recommend that enucleation be performed for IIRC Groups D and E eyes when the other eye is normal or Group A [*Consensus*].
5. We recommend that therapy aimed at saving the affected eye remain the exception for IIRC Group C and D eyes, when the other eye is normal or Group A [*Consensus*].
6. We recommend that upfront enucleation *without* pre-enucleation chemotherapy be performed for any IIRC Group E eyes, which impose risk for difficult-to-treat systemic metastases. Pre-enucleation chemotherapy is dangerous, since it may mask features of extraocular extension causing understaging and undertreating of systemic disease [*Level 2*].[93]
7. We recommend enucleation for recurrent tumours when all other treatment modalities (including EBR) have failed, to prevent tumour spread outside the eye or when complications prevent evaluation and treatment of progressive disease [*Consensus*].
8. We recommend cryotherapy for the treatment of small peripheral Rb, and (or) laser therapy for small posterior Rb, primarily in IIRC Groups A, B, and C eyes, or for recurrences after other therapy [*Consensus*].
9. We recommend that cryotherapy through a conjunctival incision may be used for posterior Rb refractory to laser focal therapy [*Consensus*].
10. We recommend the use of pre-chemotherapy cryotherapy 24–72 hours before chemotherapy to increase drug penetration into the eye, particularly for vitreous seeding, but not in the presence of retinal detachment [*Consensus*].

Chemotherapy

11. We recommend that Rb patients be invited to participate in any appropriate available clinical trial [*Consensus*].
12. We recommend that chemotherapy consolidated by focal therapy replace primary EBR [*Level 2*].[47]
13. We recommend systemic chemotherapy for the primary treatment of bilateral IIRC Group B, C, or D eyes and limited therapy for unilateral IIRC Group B or C eyes with good visual potential [*Consensus*].

Radiotherapy

14. We recommend that radiotherapy be used only as salvage therapy for the remaining eye after chemotherapy and focal therapy have failed to control the tumour [*Consensus*].

Extraocular disease

15. We recommend that the Rb specialist involved in the child's case review the pathological features of every

enucleated eye for high-risk features, including invasion of optic nerve, sclera, choroid or anterior segment, that could predispose to extraocular disease or metastasis [*Level 2*].[122]

16. When high-risk features are observed, including invasion of optic nerve, sclera, choroid, or anterior segment, we recommend treatment with prophylactic chemotherapy, preferably with enrolment in a clinical study [*Level 2*].[122]
17. We recommend that metastatic and extraocular (orbital) disease be treated on a clinical trial, if available [*Consensus*].
18. We recommend that extraocular Rb treatment protocols generally include, but not be limited to, orbital radiation for orbital recurrence postenucleation, systemic chemotherapy, stem cell/bone marrow transplant after a good response to systemic chemotherapy, and intrathecal chemotherapy for CNS disease with meningeal spread [*Level 2*].[123]
19. If Rb metastasis is present in bone marrow, bone, or other organs or tissues, we recommend enucleation of the eye, adjunctive chemotherapy and hematopoetic stem cell transplant if there is a chemotherapy response [*Level 2*].[123]
20. If Rb extends into the orbit, to the cut end of the optic nerve, optic chiasm or brain, we recommend enucleation of the eye, adjunctive chemotherapy, extended doses of intrathecal chemotherapy, irradiation of the involved tissues, followed by hematopoetic stem cell transplant if there is a chemotherapy response [*Level 2*].[123]
21. If the Rb tumour involves the meninges of the brain and spinal cord, we recommend palliative treatment [*Consensus*].
22. We do not recommend exenteration of the orbit for Rb, since chemotherapy will provide more effective palliation, even for massive proptosis [*Level 2*].[124]
23. If Rb tumour cells are found in the CSF, we recommend enucleation of the eye, adjuvant chemotherapy, hematopoetic stem cell transplant if there is a chemotherapy response, and 3 years of periodic intrathecal chemotherapy [*Consensus*].

FOLLOW-UP

Introduction

The last decade has seen tremendous advances in the body of knowledge about childhood cancer, and major changes in the technologies used to treat it. Survival rates have increased dramatically over the last 40 years. The 2008 Canadian cancer statistics show an overall cure rate of 82% for children 0–14 years old.[125] The global population of childhood cancer survivors is therefore growing. Since retinoblastoma (Rb) is curable by timely removal of the eye(s) with tumour, survival of Rb is greater than 95% in developed countries. Even the small proportion of children with metastatic Rb now has some hope for cure, with new therapies that include high-dose chemotherapy and autologous hematopoietic stem cell rescue.

Starting in the 1960s, cure of Rb while saving eyes and vision was achieved by the widespread primary treatment with external beam radiation (EBR). Sadly, years later it was recognized that the inherent risk of secondary non-Rb cancers in persons with constitutional mutations of one allele of the *RB1* gene was markedly increased by radiation. The risk of dying from a secondary non-Rb cancer became much higher than of dying of the initial Rb. In the 1990s, chemotherapy largely replaced radiation as primary treatment for intraocular Rb; 18 years later, major long-term side effects of chemotherapy have not become evident.

All survivors of childhood cancer face potential chronic health issues. It is estimated that 58% all childhood cancer survivors suffer at least 1 chronic medical problem; 32% suffer 2 or more;[126,127] and 44% reported at least 1 health issue adversely affected by their childhood cancer.[128]

Systematic follow-up care for childhood cancer survivors has many positive benefits, including late effects monitoring, surveillance of ongoing health issues and secondary non-Rb cancer, health promotion, counselling, and participation in research. Potential barriers to long-term follow-up include inadequate resources, patient lack of awareness, and lack of awareness within the adult care system of the needs of childhood cancer survivors, particularly those with very specialized needs, such as Rb survivors. Access to ongoing specialist or focused care is very dependent upon location and local interest.[129]

In this chapter, we recommend a systematic approach to the clinical follow-up of Rb survivors. We emphasize the need to educate and empower survivors after transitioning from a pediatric service, to seek out appropriate healthcare professionals to coordinate their ongoing care.

Definitions

Active follow-up

During active follow-up, the emphasis is on ophthalmic surveillance for new and recurrent Rb tumours, visual rehabilitation, and medium-term monitoring of late effects of treatments. For Rb, we define active follow-up as the time from the last active Rb treatment (whether chemotherapy, radiotherapy, local therapy, or hematopoietic stem cell transplantation) until age 9 years, or 5 years after the last active treatment is performed. This includes surveillance for recurrent disease and new Rb tumours in the eyes, and monitoring and treating treatment-related side effects. The active follow-up period does not involve active treatment for Rb (see "Treatment" chapter).

Long-term follow-up

Long-term follow-up for Rb covers the period of follow-up after 9 years of age or beyond 5 years after the last active treatment. These patients have no evidence of active disease

and risk of relapse is minimal. Long-term follow-up focuses upon survivorship, monitoring of late effects of cancer treatments, ongoing ophthalmological care, genetic counselling, and surveillance for secondary non-Rb malignancy.

Late effects

Late effects refer to "therapy-related complications" or "adverse effects" causally related to treatment of cancer that persist or arise after treatment has finished. These may be related to surgery, chemotherapy and (or) radiotherapy. There may also be sequelae related to the original cancer, and psychosocial issues relating to the package of treatment received.

Survivorship

Survivors are individuals who have been diagnosed and treated for cancer. Survivors may also be family members and friends who have shared the experience of cancer. Survivorship is the whole experience of living with and beyond the diagnosis and treatment of cancer. According to the United States National Cancer Institute (NCI) Office of Cancer Survivorship, *"An individual is considered a cancer survivor from the time of diagnosis, through the balance of his or her life. Family members, friends, and caregivers are also impacted by the survivorship experience and are therefore included in this definition.*"

Ophthalmology Follow-Up

Inadequate active surveillance of eyes post-treatment may contribute to late diagnosis of recurrence, new tumours or missed treatment-related side effects. Examination under anaesthesia (EUA) or dilated eye examinations are required.

Examination under anaesthesia

EUA for full retinal examination is required to monitor tumour activity and recurrence in children with eyes that have treated tumours, usually for children under 3 years of age, or older children if anterior tumours were originally present. The pediatric anaesthetist who regularly works with the Rb team greatly facilitates the procedures and assists the children in coping with the repeated EUAs, extending the first years of their lives. During active treatment and early follow-up, intervals between EUAs can be as short as 3 weeks, with longer intervals as tumour activity and risk of recurrence decrease. Recurrent and (or) new tumours in the eyes are expected in the first years after treatment of intraocular Rb, particularly in patients with constitutional germline *RB1* mutations (see "Genetic Analysis" chapter).[130] The multidisciplinary team may then choose to control small tumours with focal therapy, or even chemotherapy, if indicated (see "Treatment" chapter).

EUAs will continue until the team is convinced that the risk for tumour recurrence or new tumours is minimal; i.e., when the tumours have been inactive for 8 to 12 months (and required no focal laser or cryotherapy during that time), and the child with a germline *RB1* mutation is over 3 years of age. Follow-up can continue with full pupillary dilation in the eye clinic, as long as the child can cooperate. Late-onset new tumours tend to develop in the peripheral retina, where they have lesser impact on vision,[130] but are more difficult to visualize completely on dilated eye examinations in the eye clinic, and therefore may require EUA. A visual acuity assessment and examination of an enucleated socket can occur at each clinic visit and EUA. Regular refractions at EUA can help detect refractive errors that might be overlooked while focusing on disease control. The assistance of an ocularist or an orbital surgeon may help with issues related to the enucleated eye socket.

Eye clinic visits

When the child is ready for transition from EUA to the eye clinic, regular (every 6 months) ocular assessment is important until the age of 9 years. Clinical examination includes vision assessment, examination of the retina with the pupil fully dilated, refraction, and assessment of ocular alignment.

The eyes are also evaluated for complications of focal therapy or radiotherapy, such as keratopathy (corneal dryness and erosions) or cataract. Laser therapy through an incompletely dilated pupil may cause atrophy of the pupillary margin of the iris (posterior senechiae). Excessive laser may also cause gliosis, vitreous hemorrhages and condensation, retinal detachment, tumour seeding or cataracts.[99] Retinal detachment is a known immediate complication of cryotherapy that can be hard to treat in eyes with Rb. Detachment may resolve as the tumour regresses, but many remain long term, resulting in loss of vision. Surgical reattachment of the retina may be performed when there is no evidence of active Rb for at least a year.

The visual potential of an eye compromised by scars can be maximized by treatment such as patching of the better-seeing eye to prevent amblyopia.[131] Lenses made from a shatterproof material, such as polycarbonate, are often prescribed to protect the only eye of a functionally uniocular child from trauma. Without constant use, the protective capacity of such eyewear is reduced. If an eye has been removed, the socket is examined (see "Follow-up for enucleated socket" section, below). From age 9 to 15 years, eye clinic visits are annual. After age 15 years, the eye clinic visits are scheduled every 2 to 3 years for the rest of the patient's life (Fig. 6).

Follow-up for enucleated socket

Management of an enucleated socket starts at enucleation, and continues with every subsequent EUA and clinic visit. Follow-up includes examination for infection, implant exposure or extrusion, and fit of the prosthetic eye. Socket infections are cultured and treated with appropriate antibiotics. Orbital implant exposures or extrusions are scheduled for prompt repair. Repeated infection and discharge may occasionally require replacement of the implant, especially the porous implants. A dermis fat graft may solve the problem of the chronically irritated implant. The prosthesis

is cleaned using regular soap and water before it is replaced at the end of the examination. The ocularist will regularly check, polish, enlarge, or replace the prosthesis. Ultimately, the family and child are taught how to remove and care for the prosthetic eye.

Vision rehabilitation and support

Rb survivors of school age with significantly reduced visual fields or visual acuity less than 6/12 may be offered visual assessment to optimize a plan for aids and resources.[132] Children and adults with visual impairment can benefit from communication with mentors who have similar visual impairments. The Canadian National Institute for the Blind (CNIB) can assist with low-vision assessment, equipment, and programs to optimize education, employment, and life experiences.

Oncology Follow-Up

All children who have received adjunctive chemotherapy, radiotherapy or autologous hematopoetic stem cell transplantation require ongoing oncology follow-up to monitor for relapse of disease and late effects related to therapies they received. Conventionally, this process may be conceptually divided into active and long-term follow-up, although in reality there is overlap between these two, and the emphasis of follow-up changes over time for each patient.

General oncology follow-up

Evidence-based guidelines for general follow-up of cancer survivors are available including the Children's Oncology Survivorship Guidelines,[133] the United Kingdom Children's Cancer and Leukemia Group Follow-up Practice Statement,[134] the Scottish Intercollegiate Guidelines Network[135] and follow-up guidelines incorporated in clinical trials. The following section describes suggested follow-up for children treated for various scenarios of Rb disease and treatment.

Children who have NOT been treated with chemotherapy

Children with unilateral Rb who undergo primary enucleation and test negative in blood for the *RB1* mutations discovered in their tumour do not require oncology follow-up, since they did not undergo chemotherapy and their risk of secondary non-Rb cancer is close to the normal population risk.

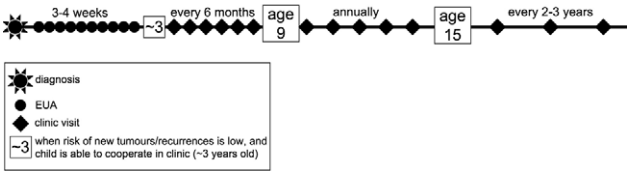

Figure 6–Schedule of EUA and clinic visits for children with Rb. Immediately upon diagnosis, the child will be seen for EUA every 3 to 4 weeks, depending on the extent of tumour activity. When Rb tumours remain inactive after treatment for a significant period of time, and the risk is low for new tumours and (or) recurrences, the active follow-up for surveillance of new tumours can transition to the clinic, as long as the child can cooperate (at approximately 3 years of age), with examination every 6 months. After age 9, long-term follow-up begins, with annual clinic visits. After age 15, clinic visits may occur every 2–3 years, for the lifetime of the patient.

In addition to genetic counselling (see "Genetic Analysis" chapter), all children with *RB1* germline mutations benefit from regular oncology clinic follow-up until age 18 years, when follow-up is transferred to an alternative follow-up program as locally available. Each oncology clinic visit also includes counselling for the parents and the children as they grow up (see "Secondary non-Rb malignancy risk counselling" section).

Children who have been treated with chemotherapy

Active follow-up in the oncology clinic for Rb survivors occurs in the 5 years post-completion of chemotherapy, at 3- to 6-month intervals. Long-term follow-up in the oncology clinic occurs every 1–2 years until approximately 18 years of age, when follow-up in an adult follow-up program is preferable, if available.

Each oncology clinic visit includes updated medical history, weight, height and vital signs assessment, physical examination, developmental and educational history, complete blood count (CBC), including differential count and platelet count. Depending on the chemotherapy regimen received, additional late effects monitoring may be performed. Most children treated with chemotherapy for Rb will at present receive combinations of carboplatin, etoposide and vincristine alone. Additional agents will usually be administered under the aegis of clinical trials, which will include late effects monitoring recommendations.

Monitoring may include surveillance for the following drug-specific complications:

Carboplatin

- Ototoxicity: Carboplatin carries small risks of high-tone hearing loss, which may require hearing aids. Serial pure-tone audiograms (including high-frequency testing) are used to monitor for hearing deficits. Hearing should be tested 3 months after completion of chemotherapy, then every 1–5 years as clinically appropriate.
- Nephrotoxicity: There is a small risk of renal tubular or glomerular damage by carboplatin, which may be monitored by renal function testing. Baseline blood urea nitrogen (BUN), creatinine and electrolyte measurements are tested 3 months after completion of chemotherapy and then annually as clinically appropriate. Glomerular filtration rate (GFR) (by radionuclide scan or by 24-hour urine creatinine clearance) is tested after completion of chemotherapy and then at 5-year intervals as clinically appropriate. Blood pressure is monitored yearly.
- Secondary non-Rb cancer: Carboplatin carries a very small risk of secondary myelodysplasia/myeloid leukemia. This risk is less than that with etoposide, but may be present for longer.

Etoposide

- Secondary non-Rb cancer: Etoposide carries a low risk of secondary acute myeloid leukemia or myelodysplasia. The risk is greatest during the 2 years following therapy, then decreases.[115,136] Serial CBC is monitored at least yearly for 10 years due to the risk of secondary acute myeloid leukemia, and then as clinically indicated.

Vincristine

- Neuropathy: Vincristine causes peripheral neuropathies, which almost always resolve with time. Symptoms of pins and needles and loss of deep tendon reflexes are rare but possible, and usually resolve. Survivors should be monitored by history and examination during routine examinations for persistence of peripheral neuropathy.

Children with high-risk clinical and pathological features in enucleated eyes

High-risk clinical and pathological features in enucleated eyes put patients at risk for Rb spread outside the eye, most commonly to bone marrow, and rarely to other organs (systemic metastases), or into the central nervous system (CNS) and cerebrospinal fluid (CSF).

High-risk clinical features, as defined by the 2009 Tumor, Node, Metastasis (TNM) Classification,[87] include:

T4: Severe local disease

- T4a: Invasion of optic nerve.
- T4b: Invasion into the orbit.
- T4c: Intracranial extension not past chiasm.
- T4d: Intracranial extension past chiasm.

High-risk pathological features, as defined by the 2009 TNM Classification,[87] include:

pT2: Tumour with minimal optic nerve and (or) choroidal invasion

- pT2a: Tumour superficially invades optic nerve head but does not extend past lamina cribrosa **or** tumour exhibits focal choroidal invasion.
- pT2b: Tumour superficially invades optic nerve head but does not extend past lamina cribrosa **and** exhibits focal choroidal invasion.

Children with extremely high-risk pathological features in an enucleated eye

Extremely high-risk pathological features as defined by the 2009 TNM Classification[87] require more intensive follow-up and surveillance for potential metastasis, and include:

pT3: Tumour with significant optic nerve and (or) choroidal invasion

- pT3a: Tumour invades optic nerve past lamina cribrosa but not to surgical resection line **or** tumour exhibits massive choroidal invasion > 3 mm in any dimension.
- pT3b: Tumour invades optic nerve past lamina cribrosa but not to surgical resection line **and** exhibits massive choroidal invasion > 3 mm in any dimension.

pT4: Tumour invades optic nerve to resection line or exhibits extraocular extension elsewhere:

- pT4a: Tumour invades optic nerve to resection line but no extraocular extension identified.
- pT4b: Tumour invades optic nerve to resection line and extraocular extension identified.

All patients at high or extremely high risk for CNS or systemic metastases because of adverse pathological features of enucleated eyes undergo ongoing surveillance for up to 5 years, with periodic (every 3–8 months) lumbar punctures, and the following additional measures only for patients at extremely high risk: bilateral posterior iliac spine bone marrow aspirates, MRI of the head and orbits and whole-body MRI.[89] MRI is preferable to CT for follow-up, in order to reduce exposure to diagnostic radiation, which incurs an increased risk of secondary non-Rb malignancies.[88] Although whole-body MRI is presently not widely available, the MRI equipment available in most institutions could be used for this study provided a fast spin-echo (FSE) short inversion time inversion recovery (STIR) protocol is used to rapidly screen T2-weighted sequences of the entire body.[90]

Children with metastatic spread or trilateral retinoblastoma disease

Children with clinical evidence of metastatic spread are defined by the 2008 TNM Classification[137] as:

M1: Systemic Metastasis

- M1a: Single lesion to sites other than CNS.
- M1b: Multiple lesions to sites other than CNS.
- M1c: Prechiasmatic CNS lesion(s).
- M1d: Postchiasmatic CNS lesion(s).
- M1e: Leptomeningeal and /or CSF involvement.

Children who have established metastatic spread, either systemically or to CNS, or children with trilateral tumours, will have undergone intensive therapy, usually involving high-dose chemotherapy and hematopoietic stem cell transplant (see "Treatment" chapter), possibly following a clinical trial. Their follow-up will need to be individualized to consider additional toxicities associated with these treatments.

Follow-Up for Detection of Trilateral Retinoblastoma or Secondary Non-Retinoblastoma Cancer

Children with germline *RB1* mutations are predisposed to trilateral Rb. However, considering its rarity, repeated screening for trilateral Rb by MRI of the head and orbits after the first negative MRI is not practical in Canada today.

Though the risk of secondary non-Rb cancer is high in this cohort of patients, whole-body MRI for detection of secondary non-Rb cancer is not feasible and has not been validated by clinical trials. The most effective emphasis today may be secondary non-Rb malignancy risk counselling.

Secondary non-Rb malignancy risk counselling

All survivors of childhood cancer have an increased secondary non-Rb malignancy risk,[138] and require counselling.

However, this risk is dependent upon many factors, including underlying disease, genetic and family history, and the treatments received, including exposure to chemotherapy and radiotherapy treatments.[139,140]

Patients without germline RB1 *mutations*

Survivors who have unilateral disease, with no germline *RB1* mutation detected, and who have received no additional therapies have a secondary non-Rb malignancy risk that is close to that of the normal population and require little or no additional counselling.

Survivors who have received adjunctive chemotherapy should be counselled on the slightly increased risk of secondary non-Rb malignancy according to the chemotherapy agents to which they have been exposed (see "General Oncology Follow-Up" section).

Patients with germline RB1 mutations

Persons carrying *RB1* mutations (see "Genetic Analysis" chapter) are at an increased risk of secondary non-Rb malignancy, and should be advised as follows:

- They have a lifelong risk of cancer because they have a defective *RB1* gene.[60]
- Osteosarcoma, soft-tissue sarcomas, malignant melanoma, brain tumours including gliomas and glioblastoma multiforme, and adult malignancies such as lung, bladder or other carcinomas are more likely for them than other people.
- Potential factors that could further increase their risk of cancer include smoking, second-hand smoke, diagnostic radiation (other health issues may override the risks and support use of diagnostic radiation), excessive UV-radiation exposure and other DNA-damaging agents.
- A diet rich in natural antioxidants naturally present in green, yellow, red, and orange fruits and vegetables, especially green leafy and cruciferous (cabbage family) vegetables, may minimize the damage to DNA that leads to cancer and reduce the risk of future cancer development.
- Repeated diagnostic imaging or other tests to screen for such potential secondary non-Rb cancers is *not* a reasonable approach.
- It is important to maintain a high index of suspicion and increased vigilance for any unexplained or unexpected symptoms and signs that might signal cancer; e.g., bone pain, unexplained lump.
- Early diagnosis and timely treatment give the best chance of cure.
- Patients should inform their doctors that they carry a mutation in the *RB1* tumour suppressor gene, and that any necessary imaging should be carried out with ultrasonography and MRI, rather than radiation-based modalities such as CT scan or X-ray.
- Genetic counselling is important for the *RB1* mutation carrier and their relatives (see "Genetic Analysis" chapter).

Patients with germline RB1 *mutations who have received radiation*

Rb survivors who have germline *RB1* gene mutations (see "Genetic Analysis" chapter) are at an increased risk for development of secondary non-Rb tumours, particularly if they were treated with radiation,[48–51,59,60,78,79,116,117,141-149] necessitating long-term follow-up.

Persons who received radiation therapy may benefit from additional counselling informing them that while radiation was needed to save the eye or life, the treatment induced a lifelong increase in risk for subsequent non-Rb cancer, particularly within the radiation field. Therefore, they are advised to maintain a high index of suspicion and surveillance for the possibility of such a radiation-induced secondary non-Rb cancer.

Radiation-induced secondary non-Rb malignancies are particularly common if patients are irradiated in the first year of life. However, children treated over the age of 1 year with an *RB1* mutation still remain at risk of radiation-induced secondary non-Rb malignancies.[61] Furthermore, the high risk of both radiation-induced and sporadic secondary non-Rb malignancies is lifelong for persons with *RB1* germline mutations. The radiation-induced secondary non-Rb malignancies include osteosarcoma, soft-tissue sarcoma, glioblastoma multiforme and other malignant brain tumours, and malignant melanoma. In addition to these tumours, the sporadic secondary non-Rb malignancies also include adult cancers such as lung, bladder, thyroid, and other types of carcinoma.[60]

The introduction of newer radiation techniques, such as stereotactic radiotherapy, IMRT, local plaque brachytherapy and proton beam radiotherapy, may reduce the radiation exposure to surrounding tissues and help to reduce the risk of secondary malignancy and other radiation-induced late effects.[119,120,150,151]

Lifelong active surveillance for secondary non-Rb malignancy, however, is neither practical nor possible, for several reasons:

- the frequency of effective surveillance to achieve "early diagnosis" would have to be at least 4 times a year;
- the whole body has to be imaged for effective surveillance;
- CT scan significantly increases radiation risk,[88] so is contraindicated for surveillance, especially in persons with *RB1* mutations, and there is no whole body CT scan imaging modality;
- radionuclide bone and gallium scans also incur whole body radiation exposure;
- ultrasonography has limited utility for surveillance, and whole-body imaging is not possible; and
- whole-body MRI is available only in a few institutions.[89]

The current practical compromise is to teach "increased cancer awareness" to parents and to children as they grow up. In that way, they are encouraged to have a high index of suspicion of symptoms and signs, and are trained to act promptly and appropriately. The earlier the diagnosis of a

secondary non-Rb malignancy, the more likely treatment can cure and healthcare costs can be reduced.

Long-term follow-up counselling for parents, children as they grow up, and adult survivors of Rb includes genetic counselling, family planning and discussion of ways to minimize potential adverse treatment effects and secondary non-Rb malignancy risks. The counselling is most effective in face-to-face sessions repeated at each clinic visit, so that parents, older children and adults will have the opportunity to ask questions and request clarification. The growing and maturing child will also be progressively exposed to ongoing discussions and education about cancer awareness as they travel through the follow-up process. Concrete examples are used to illustrate the issues discussed. The goal is to ensure this information is incorporated into the lifestyles of the individuals with *RB1* germline mutations.

Other long-term radiation side effects

While radiation increases the lifelong risk of secondary non-Rb cancers in individuals with a germline *RB1* mutation, as described above,[61,79] patients should be advised on the additional long-term effects of radiation, including:

- Cosmetic growth deformities that may require craniofacial reconstructive surgery when the patient has reached full growth. Such cosmetic deformities are known to be less common with the modern radiation techniques.[121]
- Cataracts and keratopathy, for which cataract removal and remedial therapy are available.
- Endocrine late effects due to possible exposure of the pituitary gland. Although this risk is small with modern radiotherapy techniques, it may still lead to growth hormone deficiency, hypothyroidism and possible fertility problems. For this reason, patients who have received radiotherapy should receive endocrine surveillance through oncology or endocrinology clinics.

Radioactive plaque therapy to treat localized small tumours does not carry risk of inducing secondary non-Rb cancers or cosmetic growth deformities.

Survivorship

Some survivors are significantly affected by their cancer experience, whereas others feel little or no impact upon their day-to-day lives. Areas that may be affected range from health and healthcare provision, educational opportunities, employment, and personal relationships.

Though limited research has been undertaken in this field, it has been suggested that cancer survivors have poorer outcomes with regard to employability, marriage and relationships, education, and access to insurance, in addition to the visual impairment-related quality-of-life issues we recognize with Rb survivors.[128] It is therefore suggested that any long-term follow-up program include access to a multidisciplinary care team to provide not only medical and nursing care, but also psychological and social work assistance (see "Psychosocial Care and Access to Services" chapter).

FOLLOW-UP—RECOMMENDATIONS

1. We recommend that all survivors of Rb receive individualized, lifelong follow-up and surveillance, counselling, and interventions for late effects of disease and treatment, delivered by a multidisciplinary team [*Consensus*].

Ophthalmology follow-up

2. We recommend that following completion of treatment, EUAs for children at risk of developing new Rb tumours continue as often as every 3 weeks, or at longer intervals as tumour activity decreases, until risk of new tumours and recurrences are low, and the child is able to cooperate in clinic (at about 3 years of age). The frequency of examinations will be highest when the child has a proven *RB1* germline mutation. [*Level 2*] [54,56,130]
3. We recommend that following the end of EUAs, clinic visits for retinal exam should continue every 6 months to age 9, annually to age 15, and every 2–3 years thereafter for life, as illustrated in Figure 6 [*Consensus*].
4. We recommend that children shown to not carry the *RB1* mutant allele of their family through a blood test do not require EUA or intense surveillance [*Consensus*].
5. We recommend the examination of an enucleated socket for infection, fit of prosthesis and implant exposure or extrusion at every EUA and clinic visit [*Consensus*].
6. We recommend prescribing and monitoring the use of protective eyewear for children who are functionally uniocular [*Consensus*].
7. We recommend that Rb survivors of school age with significantly reduced visual fields or visual acuity less than 6/12 undergo visual assessment and referral to the Canadian National Institute for the Blind (CNIB) for additional assistance when appropriate [*Consensus*].

Oncology follow-up

8. We recommend that Rb survivors treated with chemotherapy or EBR undergo oncology clinic follow-up at 3- to 6-monthly intervals for 5 years after finishing chemotherapy, and then every 1–2 years until age 18 years, and then lifelong follow-up every 2 years in an adult oncology facility [*Consensus*].
9. We recommend that persons carrying an *RB1* germline mutation, or nongermline Rb survivors treated with chemotherapy or EBR, be seen in oncology clinic for counselling about risk of secondary non-Rb cancers, annually until age 18 years, then lifelong follow-up every 2 years in an adult oncology facility [*Consensus*].
10. We recommend that MRI replace CT scan if possible, in patients with *RB1* germline mutations, since diagnostic radiation may increase their already significant risk of secondary non-Rb malignancies [*Level 2*].[88]
11. When there is clinical or pathological evidence of risk of extraocular Rb (TNM staging), we recommend bone marrow aspirate and (or) lumbar puncture every 3 months for 3 years after the last chemotherapy [*Level 2*].[122]

12. We recommend that persons at risk for systemic metastases based on pathological examination of the enucleated eye be monitored for 5 years with periodic bone marrow aspirates, MRI of the head and orbits and whole-body MRI, if available [*Consensus*].
13. We recommend that patients at risk for CNS metastases be monitored every 3 to 8 months for 5 years, with lumbar punctures, MRI of the head, orbits and spine and whole-body MRI,[89] if available, followed by lifelong annual surveillance via an alternative follow-up program as locally available [*Consensus*].
14. We do *not* recommend oncology clinic follow-up for children with unilateral Rb, treated only by enucleation, who test negative in blood for the *RB1* mutations discovered in their tumour, since their risk of secondary non-Rb cancer is close to the normal population risk [*Consensus*].
15. We do *not* recommend repeated MRI of the head and orbits in children with a germline *RB1* mutation as screening for trilateral Rb, since this is not practical today in Canada [*Consensus*].

PSYCHOSOCIAL CARE AND ACCESS TO SERVICES

Introduction

Retinoblastoma (Rb) emerges in infancy or very early in life and presents unique psychosocial challenges to families and patients. At diagnosis, the burden falls on parents and close family members. Children are directly affected as they transition to adolescence and adulthood, when both the disease and treatment have major implications for important life choices.[152-157]

Psychosocial and financial supports for Rb families are important at the time of diagnosis, during active treatment, and throughout follow-up. Some children and families require continued support during the school years. Children with a hereditary gene mutation also need support for genetic counselling as they enter adulthood. This chapter provides an overview of psychosocial issues that may arise for Rb patients and their families. The consensus recommendations for appropriate psychosocial supports are guided by research and current best clinical practices.

Psychosocial Impacts of Pediatric Cancer

Families that are affected by a childhood cancer experience a wide range of emotions that begin at initial diagnosis, span treatment, and often persist through long-term follow-up. Uncertainties, a key cause of anxiety for many parents,[158-160] remain long after treatment is complete and the child is considered cured.[157,161] Chemotherapy and radiotherapy treatment are high-stress events, each with risks to balance potential benefits (see "Follow-up" chapter). The potential for recurrence of tumour during treatment and active follow-up raises the possibility of complex and changing treatment plans, requiring repeated parental consent. For many families, treatment depends on travel to another city and separation from precious social support networks. Travel may impose changing terms of employment for at least one parent and significant financial burdens on the family.[162-164]

The majority of psychosocial research in pediatric cancer concerns childhood leukemia. Outcomes show active support programs positively impact the long-term well-being of the child. Structured interventions reduce parental anxiety and improve both parental decision-making and treatment compliance.[158,165,166] Many parents identified access to disease and treatment-related information to be key to effective support.[167,168] Interdisciplinary healthcare teams are an effective way to meet the diverse information and psychosocial needs of childhood cancer families.[169]

The Retinoblastoma Experience

Rb diagnosis induces short-term emotional distress for the parents and long-term concerns as the child transitions to adolescence and adulthood. Emotional responses experienced by Rb parents, patients, and family members during diagnosis, treatment, short-term follow-up and long-term quality of life are studied.[157,170,171] Many Rb parents experience levels of stress and social disruption similar to parents of children with physical or developmental disabilities.[172-176]

Rb parents have described experiencing panic as they realized that something was severely wrong with their child's eye(s). The highest levels of stress arises in the first 2 months after the diagnosis of cancer.[177] Shock, anger, sadness, and disbelief are commonly reported at diagnosis.[170] Active treatment is often lengthy, generating chronic stress, sleep disturbances, and worry or anxiety about treatment decisions and the threat of recurrence. Many parents express concerns for their infant's well-being and worry how Rb will affect their own parental and caregiving role.[157,170,171,178,179]

Post-treatment anxiety and confusion centre on why Rb developed and how the parents might have prevented the disease. The growing child becomes aware of vision loss or impairment.[170,180] She/he often focuses on the loss of their eye, the ocular prosthesis, and altered facial structure caused by radiotherapy treatment.[170] Teasing or bullying frequently target the ocular prosthesis or facial asymmetry[170,180] Parents of school-aged Rb children commonly express anxiety over the integration process and the need for classroom support.[157,170] Medically related phobias may emerge during or after treatment.[157,170]

Adult Rb survivors face new and different challenges. Rb has been associated with reduced levels of education attainment, social integration, employment, and income.[157,161,181] As young adults consider having children of their own, understanding and communicating risk to future offspring is of special concern when heritable Rb is present.[182] Access to genetic counselling is critical at this period.

Access to Care

Availability and accessibility of appropriate psychosocial support complements ongoing medical treatment and checkups. A wide range of other supports—school support, genetic counselling, visual rehabilitation, financial support, palliative care, and bereavement support (described below)—are important, but often not accessible to all families in need.

A recent UK review showed that >90% of childhood cancer treatment centres employed social workers, child life/play specialists, genetic counsellors, and pediatric oncology nurses.[169] Patient-to-staff ratios varied significantly between institutions, with the largest ratios in counselling and psychological support. Lack of dedicated counselling personnel was offset by interdisciplinary treatment teams that used the considerable crossover between the staff roles to provide individual and family care. In shared-care situations, external professionals often provided support for Rb families.[169] Clinical psychologists were rarely included on childhood cancer treatment teams.[169,183]

Components of Psychosocial Care

Patient and family support—family-centred care model

Family-centred healthcare is an approach that acknowledges the vital role families play in a child's well-being. This model of care promotes effective parental decision-making while respecting family and cultural values and beliefs. Mothers and fathers are encouraged to share and actively participate in caregiving during their child's hospitalization. Family-centred care depends on a comprehensive assessment including language and communication styles, family and societal issues, psychosocial stressors, and health beliefs and practices.[184] Optimal care is provided by interdisciplinary teams.[185] The importance of attentive and interactive care during the diagnosis stage is of particular importance to Rb parents. When parents' reasons for first seeking medical attention are minimized and (or) disregarded, there is a greater likelihood of reduced adherence to treatment. This can negatively affect the long-term well-being of the child.[170]

Structured psychosocial assessment and care during treatment

The presentation of Rb in infancy or early childhood exposes the child and family to significant social disruption and psychosocial stress. Rb parents benefited greatly when psychosocial support was provided at diagnosis, throughout active treatment, and post-treatment. The best outcomes were obtained when such supports were integrated with medical treatment.[170]

Providing initial and ongoing psychosocial support services is a clearly established component of care in designated UK childhood cancer treatment centres. However, few formal standard practices and procedures were documented in a review of this system.[169] The team approach with overlapping support roles for healthcare professionals may be considered "best practice," but often lacked formal documentation and varied in degree of implementation. For example, >75% of the studied treatment centres rely on informal psychosocial assessments at intake. Most centres embark on formal assessment only if a specific need is identified. These were usually performed by social workers. Existing support programs typically focus on patients and parents. Few support resources are available for siblings and other family members.[169]

Child life

Child life specialists are experts in child development who promote effective coping through play, preparation, education, and self-expression activities. They provide emotional support for families and children facing challenging experiences during hospitalization. The American Academy of Pediatrics affirms that child life is an essential component in quality pediatric healthcare,[186] and most institutions providing treatment for childhood cancer have child life specialists on their multidisciplinary teams.

Child life interventions often rely on focused play and self-expression activities to help the child to identify and understand the wide variety of emotions they experience during treatment.[185] Working directly with Rb children, child life specialists can provide focused support and preparation for medical procedures, increasing the child's compliance with treatment while reducing their anxiety and discomfort.

Communication Tools

Effective parent-doctor communication is highly valued by parents and families. It is shown to significantly decrease parental and family stress.[187] Most Rb parents preferred to speak directly with the treating ophthalmologist, but recognized limitations on physician availability, and relied on nursing staff and social workers for most information and explanations.[188] Parents often needed to revisit details of their child's diagnosis and treatment to better understand Rb and potential outcomes.[185] This level of understanding is an important part of fully informed consent.[91]

Written information as standard practice best addresses information needs of Rb parents. However, the information must be accurate and appropriately written for the parents' level of education. The UK survey found information availability and format varied by treatment centre. Feedback from parents was used by 60% of the surveyed centres to improve content and quality of information, and 75% of centres provided translations and interpretations.[169]

The internet has dramatically improved access to information. Online resources are highly utilized by many Rb families. They locate treatment centres, explore leading edge or experimental treatments, and identify community support resources. The majority of parents identify online resources as helpful, but less reliable or trusted, and prefer printed materials. Informal social networks between Rb parents and families are often established and maintained through email and web-based communication tools. These

relationships are important sources of information and support.[185,188]

Recent Rb research identified a cluster of parental risk factors that impact the understanding of complex medical information that may in turn influence the informed consent process.[91] Language fluency significantly affects parental understanding of Rb treatment and risk. Physician language fluency may also impact effective communication with parents. This finding underlines the importance of readily available language translation services whenever parent-physician communication involves informed consent. Further, younger parents were at greater risk of not fully understanding treatment complexity, even with high levels of education. Presenting a visual timeline of treatment allowed parents with high school or less education to quickly and accurately understand the complexity and risk of treatment, potentially offsetting the disadvantage of lower education. Parents are at greatest risk of misconceptions about treatment and risk at the time of diagnosis, just when they are required to provide fully informed consent. Extra care at this critical time is important to ensure parents receive satisfactory answers to all questions for fully informed consent.

Support groups

Pediatric cancer support groups vary in structure, purpose, and focus. Availability is based on both patient population and skilled leadership. Support groups for parents remain the most common, but specialized support groups have developed to address specific group needs and concerns. Many local and national organizations provide funding, settings, and leadership for these groups.[189] In the UK, social workers and nursing staff provide leadership for most onsite groups. Families are also referred to voluntary sector organizations. Barriers to participation included availability of group, parental time constraints, lack of available or affordable childcare, distance and transportation concerns, and feeling uncomfortable disclosing personal feelings in a group setting.[185]

In Canada, geographical dispersion of families decreases availability of support groups. Social workers conduct support groups at Rb treatment centres with a large patient population. When possible, parents are referred to local service clubs that offer support groups. Parent/family days or weekends are an effective way of bringing individuals and families together with the goal of providing support and education, often with a recreational component. These support events are often sponsored by organizations affiliated with the treatment centre, or by specific childhood cancer groups.[185] The Canadian Retinoblastoma Society (http://www.rbsociety.ca/) provides this major education and support resource for Rb families.

Long-term psychosocial support

Advances in modern medicine have improved the survival rates of children with cancer. Increased survivorship often means childhood cancer events are treated much like a chronic illness, albeit with a less certain future.[185] Half of the UK pediatric oncology treatment centres provided ongoing psychosocial support for survivors and their families, usually through the consultant oncologist. Support varied from open-door policies to regular clinical checkups. Formal policies and procedures were rare.[169] A similar pattern of support is provided in tertiary Canadian treatment centres. Oncologists and their teams are often, and informally, the point-of-contact for long-term support. Genetic counsellors also provide long-term support for families affected with heritable Rb.

Survivorship

Re-educating Rb survivors about their diagnosis and treatment as they get older is extremely important. Easy access and open communication with a medical expert is vital. Young Rb adults often have questions about late effects of treatment, risk of secondary non-Rb malignancies, and risk to future offspring.[185] Young adults may be challenged by issues of disclosure to a potential partner/spouse with respect to risk to future offspring. Medical disclosure may also impact insurability or premiums.[185,190] However, the Genetic Information Nondiscrimination Act (GINA)[2] passed by the United States Senate in May 2008 may inspire similar laws preventing this in Canada.

Transition support to school

Schools may provide education assistants and (or) teachers specializing in visual impairment. Effective communication with the staff is important as Rb children make the transition to school. Interventions focus on identifying necessary classroom supports, and educating school staff (and classmates, if appropriate) about vision status, the prosthetic eye, and advice about contact sports and wearing protective eyewear to guard against accidental injury of the only eye. Written information for schools and teachers should be a best practice.[152,155,156,172] In the UK, a majority of treatment centres (75%) had written procedures for school transition support. However, fewer than half of the procedures were developed through formal processes. Over 90% of centres designated pediatric nurses, social workers, and (or) play specialists to provide outreach services to Rb families through home visits and telephone support.[169]

In Canada, transition support is provided through a variety of local and regional hospital, service club, and publicly funded programs. Rb teams may also refer families to appropriate vision resource programs operated by the Canadian National Institute for the Blind (CNIB), visual rehabilitation services offered by agencies or service clubs, and assistive device programs operated by provincial governments.

Genetic testing and counselling

Genetic counselling can aid the informed consent process[191] and increase the likelihood that individuals will attend available support groups.[192] Availability of genetic

counselling is most relevant to Rb children and families at diagnosis and again in early adulthood. At diagnosis, genetic screening will determine to what extent the child and other siblings are affected. Testing and counselling can guide current treatment decisions and help parents make informed choices on future children. Young adult bilateral Rb survivors must consider the possibility that their own children will be at risk for Rb. If they have heritable Rb and choose to have children, counselling can inform decisions on pre- and postnatal Rb care. Available options may raise certain ethical and emotional dilemmas for some individuals. These are best addressed through discussion with a genetic counsellor (see "Genetic Analysis" chapter).

Financial support

Unanticipated costs associated with Rb treatment can be a major stressor for families. Travel costs and accommodation near the treatment centre are problematic for many families.[169] In Canada, financial support for treatment-related costs varies by province. Most families have access to provincial needs-based programs that cover at least a portion of travel and accommodation costs associated with referral to a regional treatment centre. Some programs cover the costs upfront, while others reimburse for expenses. Team social workers assist families with program contacts, and advocate on their behalf when necessary. Families may access service organizations and clubs that provide financial supports (e.g., Ronald McDonald House or Lions Club). Provincial programs provide financial supports to qualifying special-needs families (e.g., Ontario's Assistive Devices Program [ADP] and Assistance to Children with Severe Disabilities Program [ACSD]).[193,194]

Palliative care

Effective palliative care must address psychosocial needs of the family, including sibling support, school intervention, spiritual support, anticipatory grief counselling, and bereavement follow-up.[35] Access is often a barrier as many communities do not offer specialized palliative care for children. Treatment-related issues may be barriers to timely and appropriate use of a palliative care model. Physicians and parents may find it difficult to forego further efforts at curative treatments.[195] Community-based palliative care is uncommon because few primary care physicians or general and subspecialty pediatricians are trained to provide palliative care to children.[35] Home-based palliative care requires community-based nurses to act as continuous caregivers to the child and family. This care model often extends to bereavement support.[196]

Bereavement support

Bereavement support provides flexible, needs-based support and education to families following the death of their child.[185] Counselling and peer support services are generally available in the community. Support materials for parents, siblings, and other family members are available through books, videotapes, and websites. Physician contact with parents immediately following the child's death is especially important. Families have a specific need for reassurance that everything possible had been done for their child.[197]

PSYCHOSOCIAL CARE AND ACCESS TO SERVICES—RECOMMENDATIONS

1. We recommend that ongoing psychosocial support and timely and equal access to care is important for all Rb children and their families [*Consensus*].
2. We recommend that Rb families have easy and equitable access to [*Consensus*]:

- A social worker or clinical psychologist with Rb or childhood cancer expertise, from the time of diagnosis onwards.
- Structured psychosocial assessments at diagnosis and key points during treatment.
- A child life specialist during active treatment.
- Accurate, understandable, as-needed information in a variety of formats.
- Risk/informed consent information meeting parent language/age/education criteria.
- Advocacy services by professionals or community agencies for parents requiring additional support to access appropriate services.
- A centralized referral source providing links to hospital and community support groups.
- Long-term psychosocial support from diagnosis through adulthood.
- High-level genetic testing at certified laboratory and genetic counselling for all affected family members.
- Financial support for out-of-pocket costs related to treatment.
- Visual rehabilitation services.
- Aids for low vision.
- Prosthetic eye service.
- Pediatric palliative care and bereavement services.

PUBLIC AWARENESS AND EDUCATION

Introduction

Increased awareness and education about retinoblastoma (Rb) and its presenting symptoms may lead to earlier diagnosis, and consequently, a higher likelihood of cure and better vision potential for affected eyes. With these guidelines, we describe educational resources available to the general public and healthcare professionals, and discuss several successful Rb public awareness campaigns. We conclude with recommendations to increase Rb awareness and education in Canada.

Education for Parents

Parents, rather than healthcare professionals, are usually the first to notice the initial ocular signs of Rb. In one large study, the initial presenting sign in the vast majority of Rb

cases (80%, 1315/1632) was detected by a family member or friend.[13] Parental delay (between noting a sign and consulting a healthcare professional) was a median of 2.8 weeks (range 1–88 weeks).[12]

To inform and empower parents, public education about leukocoria (white pupil) and Rb is essential. As the time frame available for observation is much greater for parents, focusing on educating parents rather than increasing professional screening may be the most effective way to increase early detection of Rb. Educating the public on the signs and symptoms of Rb could empower parents to persuade a reluctant primary healthcare professional to refer to a specialist.

Internet resources

Many parents use the internet to research a white pupil, and arrive at their first physician visit with a great deal of good information on leukocoria and its common causes. Reliable sites (e.g., major pediatric and vision health association sites) could increase the likelihood of being a search engine "hit" by ensuring the keywords "white pupil" are used in their materials. Additionally, such sites would need to ensure the information on Rb is current and accurate. Many such sites currently contain no or inaccurate information on Rb.

Public awareness campaigns

Awareness campaigns to educate the public on the signs and symptoms of leukocoria are likely to increase the rates of early detection of Rb, and the likelihood of parents taking their child to a specialist sooner. Awareness campaigns in developing countries, where the majority of Rb cases present as advanced disease, have met with some success. Though presentation in Canada generally occurs earlier than in developing countries, awareness campaigns could reduce the number of advanced Rb cases in Canada, and lead to even earlier detection, resulting in better visual outcome.

In Brazil, a national campaign for early diagnosis of Rb was initiated in September 2002.[198] A public service announcement highlighting leukocoria as a symptom of cancer (www.tucca.org.br) was broadcast on several television stations throughout Brazil, and offered a toll-free telephone number the public could call to get more information. In addition to the television advertisement, educational materials were provided to the general public, primary healthcare workers, and ophthalmologists. Two years into the campaign, 20 cases of Rb were diagnosed as a direct result of the campaign.

Similarly, in Honduras, an Rb awareness campaign was initiated to promote early diagnosis. Information about Rb was disseminated to parents via government health clinics during the annual vaccination campaigns beginning in 2003.[199] Awareness materials included posters and flyers, and were complemented by television and radio advertisements about Rb. In the years following the campaign, the percentage of Rb patients presenting in the clinic with extraocular disease was only 35%, compared to the 75% in the 8 years prior to the start of the campaign.[199]

Increasing awareness of photoleukocoria

In Canada, a public awareness campaign to inform the public about photoleukocoria has been initiated by Maria Pezzente, mother of a child with trilateral Rb. Internationally, Maria has approached camera manufacturing and photograph developing companies to help raise awareness of leukocoria as a presenting sign of Rb. Through a simple letter and photographs demonstrating her child's leukocoria, the public is encouraged to seek care when photographs of children show photoleukocoria. This project now seeks camera manuals that will include information on leukocoria, and photo developer services will publish examples of photoleukocoria to educate their customers.

Education for Physicians

Once parents notice signs of potential Rb, their healthcare practitioners must know to respond with prompt referral. In the United Kingdom (UK), the majority of patients have to consult with >2 primary healthcare professionals before obtaining a referral to an ophthalmologist.[12] This suggests many primary healthcare professionals may not be aware of the presenting signs of Rb (see "Referral and Diagnosis" chapter.) Although similar data are not available for Canada, anecdotal evidence indicates that in many cases, referral of Rb patients to a specialist is also delayed, likely due to lack of physician awareness of Rb.

To increase awareness of the presenting signs of Rb among healthcare professionals in the UK, from 2003–2004 the Childhood Eye Cancer Trust (CHECT) targeted offices of general practitioners and pediatricians with an education campaign called "See Red" (http://www.chect.org.uk/page.php?id=32&aid=33&s=6). A simple poster, describing the correct method for how and when to administer the red reflex test (see "Screening" chapter, Table 2), was provided to healthcare professionals throughout the UK. This was followed in 2005 with an educational leaflet about Rb, sent to over 3600 UK ophthalmology departments and clinical directorates.

PUBLIC AWARENESS AND EDUCATION—RECOMMENDATIONS

1. We recommend that information on Rb be included in public healthcare packages given to new parents [*Consensus*].
2. We recommend that major pediatric and vision screening associations provide information on signs and symptoms of Rb in their print and online public information materials [*Consensus*].
3. We recommend that information about the proper performance of the red reflex test be provided to all those with a responsibility to perform this screening (pediatricians, nurses, family doctors) (see "Screening" chapter) [*Consensus*].

4. We recommend that information on signs and symptoms of Rb be provided to Canadian healthcare professionals who see young children and pregnant women in their clinics [*Consensus*].
5. We recommend that Rb education be included in the healthcare curricula [*Consensus*].

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GLOSSARY

Allele: One of two variations of a specific gene, on one of the pair of chromosomes. One allele on one chromosome is inherited from each parent.

Allen chart: Assessment tool used to measure visual acuity.

Amblyopia: A dysfunction in the processing of visual information which results in poor vision that is not correctable with glasses. Commonly known as lazy eye, and often caused by a misalignment of the eyes.

Antecedent relatives: Relatives preceding the individual concerned, i.e. parents, grandparents, aunts, and uncles, etc.

Assay: A procedure that measures the property or concentration of a specific substance or chemical.

At-risk relatives: Relatives who are at risk for developing a disease present in another member of a family.

Autologous: Pertaining to the same individual.

Bilateral retinoblastoma: Retinoblastoma that affects both eyes.

Binocular: Use of both eyes.

Brachytherapy: A form of radiation therapy where a plaque that emits radiation is implanted in the orbit in close proximity to the tumour target.

Cat's-eye pupil: The appearance of a white gleam when light is shone on the eye, often seen in cats.

Cataract: An opaque lesion or clouding that develops on the lens of the eye.

Chemotherapy: Medical treatment involving intravenous injection of drugs that kill actively dividing cells.

Child life: The promotion of effective coping and optimum development of children undergoing medical treatment through play, preparation, education, and self-expression activities that are based on natural child development.

Choroid: A vascularized layer of the eye located between the retina and the sclera.

Chromosome: A bundle of DNA. Normally, a person has 46 chromosomes: 22 pairs of chromosomes and two unpaired sex chromosomes.

Chromosome 13 deletion: The loss of DNA on chromosome 13, where the *RB1* gene is located. There may be loss of all or part of chromosome 13, as well as parts of neighbouring chromosomes.

Clinical examination: Medical inspection of a patient.

Coloboma: A gap in any of the structures of the eye.

Coats' disease: Abnormal leakage of the peripheral retinal blood vessels resulting from retinal arteriolar-venous shunts aneurysms, leading to macular exudates and retinal detachment.

Computed tomography (CT) scan: A medical imaging procedure that uses X-rays and a computer to produce three-dimensional, cross-sectional digital images of the body.

Congenital cataract: A cataract that is present at birth.

Conventional screening for retinoblastoma: Repeated eye examinations, including examination under anaesthesia (EUA), of children felt to be at risk for retinoblastoma.

Cryopreservation: Preservation of biological material by freezing.

Cryotherapy: Medical treatment consisting of using a freezing probe to encase the tumour in ice; the thaw cycle of each freeze application causes destruction of the tumour cells.

Cytogenetic analysis: The study of the appearance of chromosomes, using a microscope.

Diopter: A unit of measurement of the optical power of a lens or curved mirror.

Deoxyribonucleic acid (DNA): A nucleic acid that contains the genetic instructions used in the development and functioning of all known living organisms. DNA stores genetic information.

Descendants: Children and grandchildren of a specific person.

Disease morbidity: The prevalence (the number of people affected in a given population), incidence (the number of people diagnosed in a given time period), or severity of a disease.

E acuity card: Visual assessment tool used to measure stereo vision or depth perception.

Endocarditis: Inflammation of the endocardium.

Enophthalmos: The recession of the globe into the orbit.

Esotropia: A form of strabismus where the eye turns inward (nasal).

Examination under anaesthetic (EUA): The clinical procedure used to identify tumours in the eyes of a person with, or at risk for, retinoblastoma.

Exon: The protein-coding DNA sequence of a gene.

Exotropia: A form of strabismus where the eye turns outward (temporal).

Extended family: Grandparents, aunts, uncles, and cousins, in addition to first-degree relatives.

External beam radiation: Radiation therapy in which the radiation is delivered by a machine outside the body that aims the radiation beam at the tumour and adjacent tissues.

Familial retinoblastoma: Retinoblastoma affecting more than one member of the same family.

Fibrosis: The formation of too much fibrous tissue.

First-degree relatives: Parents, siblings, and children. (See also "Immediate family.")

Flexner-Wintersteiner rosette: A form of neural differentiation, very characteristic of retinoblastoma, resulting in spheres of cells with a deposit of hyaluronic acid in the centre.

Fluorescein angiography: The visualization of blood vessels by intravenous injection of a fluorescent dye.

Fluorescent in-situ hybridization (FISH): A technique using a fluorescence microscope to detect abnormalities in chromosomes.

Focal therapy: Medical treatment applied directly to the

affected site.

Fovea: The spot within the macula of the eye that provides the sharpest vision.

Gene: A segment of DNA—located in a particular position on a particular chromosome—that contains specific genetic information.

Genetic counselling: An educational process for individuals and families affected by or at risk for a heritable disease. A genetic counsellor is a qualified medical professional who provides information on the lifelong implications of a genetic mutation, the risk for other family members, screening for the disease, and family planning options.

Genetic testing: The process of analyzing an individual's genes to confirm, rule out, or reduce their risk that a heritable mutation is present.

Germline: The set of genetic information passed from one generation to the next.

Gliosis: The formation of excessive glial cells into a dense network of processes.

Hematopoietic: The ability to produce all different types of blood cells.

Hereditary: Passed on from a parent. For example, a disease caused by a genetic mutation, such as retinoblastoma.

Heritable: Able to be passed on to the next generation, but not necessarily inherited from a parent. For example, a disease caused by a genetic mutation that may or may not actually be passed on.

Heterochromia: The condition in which the iris of one eye is a different colour from the iris in the other eye.

Histopathology: The study of disease through microscopic study of diseased tissues.

Homer Wright rosettes: A form of neural differentiation resulting in spheres of cells with a tangle of processes in the centre.

Immediate family: Parents, siblings, and children. (See also "First-degree relatives.")

Informed consent: A situation in which, after first being advised of the need, process, benefits, and risks, an individual willingly agrees to participate in a specific activity, or allow his/her child to be involved in that activity.

Intensity modulated radiotherapy (IMRT): A type of radiation therapy that uses computer assistance to target the radiation beam to the size and shape of the tumour.

Intrathecal: Within the subarachnoid space of the brain.

Intron: A DNA sequence that interrupts the protein-coding sequence of a gene.

Karyotype: A microscope-enabled photograph of an individual's chromosomes that records the number, size, and shape of each chromosome type to identify chromosomal abnormalities.

Leukocoria: The appearance of a white pupil visible when light is shone into the eye, caused by an obstruction of the retina, as by tumour or retinal scar.

Macula: Small, specialized region of the central retina that is responsible for central vision.

Magnetic Resonance Imaging (MRI): A medical imaging procedure that uses powerful magnets, radio waves, and a computer to produce digital images of the body.

Molecular genetics: The field of biology that studies the structure and function of genes at a molecular level.

Monocular: Use of one eye.

Mosaicism: A heritable mutation that is present in only a fraction of cells throughout the body. This mutation is initiated after conception.

mRNA/Messenger RNA: RNA that carries information to DNA.

Mutation: A change in DNA sequence that damages gene function.

Necrosis: Cell death caused by injury or disease.

Non-familial retinoblastoma: Retinoblastoma that is not known to affect more than one member of the family.

Norrie's disease: Inherited eye disease caused by mutation of the NDP gene, leading to abnormal retinal development and blindness. Other symptoms include delayed development, progressive hearing loss, and problems with circulatory, digestive, respiratory, and reproductive systems.

Nucleotide: The structural unit of nucleic acids (RNA and DNA).

Null *RB1* mutant allele: An *RB1* gene that fails to produce detectable Rb protein.

Ocular prosthesis: An artificial eye.

Opacity: An opaque area on the eye, such as a cataract.

Ophthalmologist: A physician with special training and expertise on the diagnosis and treatment of eye diseases.

Optician: A non-medical practitioner trained in the preparation and dispensing of optical supplies, such as eyeglasses and contact lenses.

Optometrist: A non-medical primary healthcare provider with special training in the diagnosis and treatment of eye diseases.

Optotype: A standardized symbol used to assess visual acuity.

Orbital cellulitis: Swelling in the orbit.

Palliative care: Care aimed at reducing the severe symptoms of disease at the end-of-life stage.

Pathology: The study of disease.

Pedigree: A family tree diagram that shows how a specific disease has been inherited, and identifies family members at risk for inheritance of a predisposing mutation.

Penetrance: The probability that a heritable genetic mutation will actually result in the development of the disease in question.

Persistent Hyperplastic Primary Vitreous (PHPV): The presence of a vascularized membrane behind the lens of the eye. Presenting signs include leukocoria and microphthalmia, and eyes usually develop cataract and/or glaucoma.

Photoleukocoria: The detection of leukocoria in a photo-

graph taken using flash, usually with the red-eye reduction feature turned off.

Phthisis: Shrinking of the eye, usually due to necrosis.

Polymerase chain reaction (PCR): A technique used to increase the number of copies of a specific fragment of DNA.

Predisposition: Susceptibility to a disease due to inheritance of a genetic mutation, which may or may not result in actual development of the disease.

Prophylactic chemotherapy: Chemotherapy.

Prenatal retinoblastoma diagnosis: Identification of retinoblastoma before birth by obstetrical ultrasound.

Proband: The first known person in a family affected by a heritable disease; used here to refer to the key family member in whom molecular studies seek the identity of the *RB1* mutant allele.

Quantitative multiplex PCR: A method of performing multiple sets of polymerase chain reactions on several pieces of DNA simultaneously.

Radioactive plaque therapy: Radiation therapy in which the ionizing radiation is delivered via an implant inserted in the vicinity of the tumour.

Radiotherapy (Radiation therapy): Medical treatment that employs ionizing radiation.

***RB1* gene:** A tumour-suppressor gene that causes retinoblastoma when both copies are mutated in a cell.

***RB1* gene mutation/*RB1* mutant allele:** A heritable change in DNA sequence that damages *RB1* gene function and may cause retinoblastoma.

Rb protein: A large molecule coded for by the *RB1* gene that is important in the control of cell division and specialization in general. It specifically blocks the development of retinoblastoma in the retina.

Reciprocal translocation: The shuffling of genes (and sometimes damage to genes) that occurs when a pair of chromosomes exchange DNA.

Red reflex: The colour of the retina's reflection when the pupil is dilated and light is shone through.

Reduced penetrance *RB1* mutation: A situation in which Rb protein is identified at low levels and whereby the *RB1* gene may be partially functioning.

Retina: A specialized tissue within the eye that senses light and transmits images to the brain.

Retinoblastoma: Cancer of the retina, usually occurring in young children, caused by mutation of both *RB1* alleles in a cell of the retina.

Retinoma/Retinocytoma: A rare, benign tumour, which sometimes leads to malignant retinoblastoma.

Retinopathy of Prematurity (ROP): An eye disease that affects premature infants, which can cause retinal scarring and/or retinal detachment, possibly resulting from disorganized retinal blood vessel development.

Ribonucleic acid (RNA): A long chain of nucleotides found in cells. RNA transmits genetic information from DNA to protein and controls certain chemical processes in the cell.

RT-PCR (reverse transcriptase-PCR): A technique used to detect and measure the quantity of mRNA, which is responsible for gene expression and translates into protein.

Sclera: The opaque white outer protective layer of the eye.

Second primary cancers: Cancers subsequent to retinoblastoma that are associated with mutation of the *RB1* gene.

Sensitivity: An individual laboratory's measured ability to identify mutations for a specific genetic disease.

Sequencing: The process used to determine the order of nucleotides (the base sequences) in a DNA molecule, which in turn determines the structure of proteins encoded by that molecule.

Somatic cell mutation: A mutation that has occurred in any cell other than the germ cells (egg or sperm) and is therefore neither inherited nor passed on to children.

Sporadic: No previous evidence of a given disease occurring in a family. It is commonly misinterpreted to mean that there is no germline mutation, but many children with non-familial (sporadic) retinoblastoma have a germline mutation.

Strabismus: Lack of coordination between the eyes that causes them to look in different directions. Eyes can be esotropic or exotropic.

Sub-Tenon membrane: The thin material covering the nerves and muscles at the back of the eye.

Surveillance: Clinical assessment of children at risk for retinoblastoma, usually by EUA.

Toxocariasis: An infection caused by ingestion of viable eggs from the parasite *Toxocara catis* or *Toxocara canis*.

Trilateral Rb: Trilateral Rb patients have tumours in one or both eyes *and* a separate Rb tumour in the pituitary or suprasellar region of the brain.

Unaffected carrier: An individual who carries a heritable genetic mutation for, but has not developed, the associated disease.

Unilateral retinoblastoma: Rb affecting one eye (either left or right).

Uveitis: Inflammation of the uvea (middle layer of the eye).

Visual acuity: The acuteness or sharpness of vision.

Vitreous: The transparent viscous fluid in the centre of the eye.