Retinoblastoma

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Retinoblastoma is an aggressive eye cancer of infancy and childhood. Survival and the chance of saving vision depend on severity of disease at presentation. Retinoblastoma was the first tumour to draw attention to the genetic aetiology of cancer. Despite good understanding of its aetiology, mortality from retinoblastoma is about 70% in countries of low and middle income, where most affected children live. Poor public and medical awareness, and an absence of rigorous clinical trials to assess innovative treatments impede progress. Worldwide, most of the estimated 9000 newly diagnosed patients every year will die. However, global digital communications present opportunities to optimise standards of care for children and families affected by this rare and often devastating cancer. Parents are now leading the effort for widespread awareness of the danger of leucocoria. Genome-level technologies could make genetic testing a reality for every family affected by retinoblastoma. Best-practice guidelines, online sharing of pathological images, point-of-care data entry, multidisciplinary research, and clinical trials can reduce mortality. Most importantly, active participation of survivors and families will ensure that the whole wellbeing of the child is prioritised in any treatment plan.

Introduction

Retinoblastoma is the most common intraocular cancer of childhood. It is initiated by mutation of the *RB1* gene, which was the first described tumour-suppressor gene.[1,2,3] Constitutional loss of one *RB1* allele predisposes an individual to cancer; loss of the other allele from a developing retinal cell initiates development of retinoblastoma tumours. This prototypic malignancy has transformed the thinking about cancer.

Incidence of retinoblastoma is constant worldwide at one case per 15 000–20 000 livebirths, which corresponds to about 9000 new cases every year.[4] The disorder has no validated geographic or population hotspots. The greatest disease burden is recorded in large populations that have high birth rates, such as in Asia and Africa.[4] In Nigeria, for example, retinoblastoma is the most common eye tumour,[5] and is one of the five most frequent childhood malignancies.[6] Regions with greatest prevalence have the highest mortality—40–70% of children with retinoblastoma in Asia and Africa die, compared with 3–5% in Europe, Canada, and the USA (table 1).[4,7,13,14,17,19]

In Canada, mean age at diagnosis is 27 months (SD 18) for unilateral retinoblastoma[18] and 15 months for bilateral disease (Gallie BL, unpublished). In Kenya, mean age at diagnosis is 36 months (SD 21·4) for unilateral retinoblastoma, and 25 months (16·8) for bilateral disease.[13] A delay of more than 6 months from the first clinical sign to diagnosis is associated with 70% mortality recorded in developing countries.

However, positive change is imminent, because genome science and global communications could allow all children and families affected by retinoblastoma to have an equal opportunity for a cure. However, if welfare of the child is the main concern, to save life is more important than to save vision. In this Seminar, we draw attention to lessons learned about management of retinoblastoma and describe goals to ensure that all children with retinoblastoma receive the best possible life-saving and vision-saving care. We emphasise straightforward strategies that can greatly improve the chances of survival and quality of life of children with retinoblastoma.

Leucocoria

Leucocoria is the most common initial sign of retinoblastoma (table 1),[8,12,15,20,21] and is first apparent when the tumour is still contained within the eye. The life-threatening white tumour reflects light and blocks view of the red retina (figure 1). Retinoblastoma remains intraocular and curable for 3–6 months after the first sign of leucocoria. Leucocoria can also indicate other vision-threatening conditions—eg, Coats' disease, cataract, toxocariasis, retinopathy of prematurity—for which prompt medical attention is needed. It is first noticed by parents when the pupils of the child's eyes dilate naturally in dim light, with a beam of light shining over the parents' shoulder. Parents often have difficulty convincing health-care workers who see the child in bright surroundings of a problem. In a UK study,[20] 25% of children with leucocoria waited more than 4 weeks for primary-care referral to an ophthalmologist. Late diagnosis delays treatment, retinoblastoma spreads from the eye, and the chances of survival decrease.[16] Strabismus, poor visual tracking, glaucoma, and inflammation are other presenting signs (table 1).

Search strategy and selection criteria

We searched Medline for reports published between January, 2005, and November, 2011, and their bibliographies with the terms "retinoblastoma tumour", "retinoma", "retinoblastoma genetic testing", "retinoblastoma treatment", and "retinoblastoma chemotherapy". We included older, seminal publications that underpin understanding of retinoblastoma. We also used relevant review articles and best practice guidelines, although this Seminar is not focused on the epidemiology and clinical characteristics of retinoblastoma. We are part of the team that developed the Canadian Retinoblastoma Society's guidelines for care. In developing these guidelines, we searched for all evidence-based sources; when none existed, we used consensus conferencing of multidisciplinary retinoblastoma experts, practitioners, survivors, and their families.

	Mean age at diagnosis (months)		Mortality (%)	Cases with different first presenting signs (%)				
	Unilateral	Bilateral		Leucocoria	Proptosis	Swelling	Strabismus	Hypopyon
Europe								
All countries[7]	..	..	5–11%	..	..	..	..	..
Asia								
Malaysia[8]	..	..	..	..	22%	..	..	..
Taiwan[9]	27	16	36%	78%	17%	..	13%	..
Africa								
Mali[10]	..	..	..	..	55%	..	..	..
Nigeria[11]	31	15	..	62%	85%	30%	..	46%
Eastern Africa[12]	36	24	..	56%	30%	28%	11%	..
Kenya[13]	36	25	73%	..	..	..	..	..
North America								
Mexico[14]	31	20	11%	..	..	..	..	..
USA[15]	25	13	..	56%	..	<1%	24%	..
Canada	27*	15†	1%‡	~80%‡	0%‡	..	..	..
Central America								
Honduras[16]	..	..	35–73%	54–83%	..	..	..	..
South America								
Brazil[17]	..	..	5–22%	79%	..	10%	11%	..

*Taken from Mallipatna et al.[18] †Gallie BL, unpublished. ‡Taken from Canadian Retinoblastoma Society guidelines.[19]

Table 1: Geographical variation in age at diagnosis, mortality, and first presenting sign

Age at retinoblastoma diagnosis is a result of both the molecular basis—heritable retinoblastoma presents at a younger age than does non-heritable disease—and the medicosocial response to its symptoms and signs. The deadly effect of delay is obvious in Africa and Asia, where proptosis (protrusion of the eye from the socket due to advanced spreading of tumour into the orbit) seems to be a common presentation.[8–12] In these regions, socio-economic factors and poor recognition of the seriousness of the disease impede access to care.[24] Sadly, severe disease, the large numbers of infants, and overstressed health-care systems mean that children suffer when early detection and straightforward surgical treatment could have cured the disorder.

Flash photography can enable early detection of leucocoria (figure 1).[25] Anecdotal evidence suggests that parents who notice this photoleucocoria now commonly search the internet and promptly seek medical attention. A retinoblastoma education campaign in Honduras showed that public awareness led to early detection.[16] The nationwide awareness campaign led by the Kenyan National Retinoblastoma Strategy group is educating the public and health-care workers about implications of leucocoria.[26,27] Effectiveness of campaigns will be validated when their short-term and long-term effects on severity of disease at presentation are measured.

RB1 mutation status

Alfred Knudson advanced understanding of cancer when he analysed the long-known fact that children unilaterally affected by retinoblastoma are diagnosed at an older age than are bilaterally affected children, and formulated the hypothesis that two hits (mutational events) are rate-limiting for the development of retinoblastoma.[3] David Comings expanded the notion to include malignancy-suppressing loci, recognising that Knudson's hits might be mutations inactivating both copies of a retina-specific gene.[1] The discovery of the *RB1* gene at chromosome 13q14 in the 1980s confirmed that *RB1* was the first tumour-suppressor gene.[2,28,29]

Loss of function of *RB1* initiates retinoma and causes genomic instability,[30] but is insufficient to cause retino-blastoma. The genomic instability probably leads to changes in other genes.[31] The event that triggers malignant proliferation after mutation of *RB1* is unknown. Although Comings assumed that the retinoblastoma-causative gene would be retina-specific,[1] *RB1* loss in many other human cancers can contribute to cancer progression, presumably by loss of cell-cycle control and genomic stability.[32–35]

In both heritable and non-heritable retinoblastoma, biallelic mutations of the *RB1* tumour-suppressor gene initiate tumour growth (figure 2). In heritable retino-blastoma, the first *RB1* mutation (M1) is constitutional, predisposing the child to retinal tumours. Somatic mutations (M2) in one or more retinal cells initiate tumour growth (figure 2). Very rarely, primitive neuro-ectodermal tumours arise in the pineal or suprasellar region, leading to trilateral retinoblastoma.

All bilateral retinoblastoma is heritable, but only a small proportion of unilateral disease can be passed on to future generations (table 2). Most children with heritable retinoblastoma carry a novel mutation not detected in the
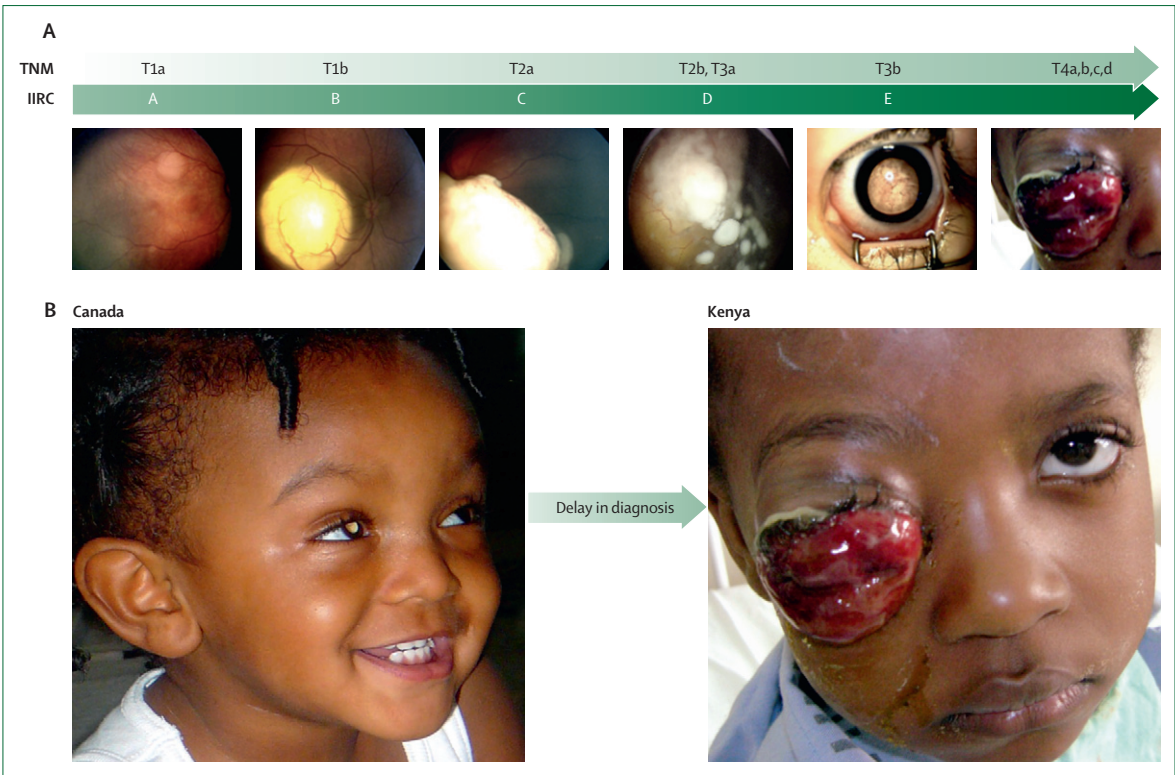
Figure 1: Progression of retinoblastoma from small intraretinal tumours to massive orbital retinoblastoma probably extending into the brain
Progression of retinoblastoma (A) from small intraretinal tumours that can be cured by laser treatment and cryotherapy (TNM T1a, IIRC A) to massive orbital retinoblastoma probably extending into the brain (TNM T4a-b). A difference in age at diagnosis recorded between Canada and Kenya could be the difference between possible cure and certain death (B). The Canadian child with leucocoria was diagnosed because of the left-hand image, which was taken by his sister with his mother's mobile phone. TNM=Tumor Node Metastasis Cancer Staging.[22] IIRC=the International Intraocular Retinoblastoma Classification.[23]
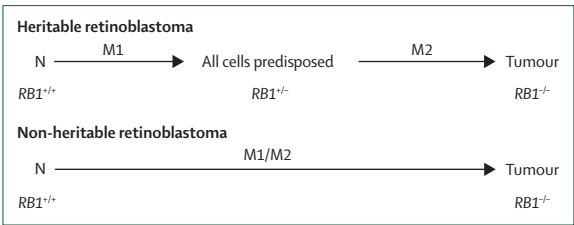

Figure 2: Genetics of heritable and non-heritable retinoblastoma
N=normal. $RB1^{+/+}$=two normal $RB1$ alleles. M1=constitutional $RB1$ mutation. $RB1^{+/-}$=one mutated, one normal $RB1$ allele. M2=somatic $RB1$ mutation. $RB1^{-/-}$=two mutated $RB1$ alleles.

	Heritable	Not heritable	Total
Bilateral retinoblastoma	40	0	40
Inherited	5	0	..
Not inherited	35	0	..
Unilateral retinoblastoma	7	52	59
Inherited	1	0	..
Not inherited	6	0	..
Unaffected carrier	1	0	1

Data taken from Richter et al.[36]

Table 2: Genetic status of 100 children with the retinoblastoma genotype or phenotype, or both

parents. 1% of the children who carry the mutation (which might or might not have been inherited) do not develop retinoblastoma tumours (unaffected carriers; table 2), although their offspring who inherit the mutation (50%) are at risk.

A constitutional *RB1* mutation also imposes an increased risk of second malignancies of the lung, bladder, bone, soft tissues, skin, and brain throughout life, especially when the children are treated with radiation.[37] New constitutional mutations arise mostly in a parental germ cell, usually paternal.[38,39] Less frequently, the *RB1* mutation arises in one cell of the multicell embryo, resulting in mosaicism in the proband.[40] Heritable retinoblastoma results, but antecedent relatives are not at risk, because mosaicism is not inherited.

Various mutations inactivate the 27 exon *RB1* gene, most of which are unique to a family, suggesting a high rate of new mutation. M1 and M2 *RB1* mutations include the full range of deleterious mutations: point mutations, small and large deletions, and deep intronic and splice mutations. The M2 mutation is identical to the M1 mutation in 52% of tumours.[36] Methylation (addition of a methyl group at CpG sites) of the promoter is a common M1 or M2 event in somatic cells, but is only a constitutional M1 event when a translocation leads to transcriptional silencing.[36,41]

Most *RB1* mutations result in an inactive retinoblastoma protein (pRB).[40] Compared with completely inactive pRB, partly inactive pRB reduces penetrance (fewer affected gene carriers) and expressivity (fewer tumours in those affected, with more unilaterally affected).[42,43] Children with loss of *RB1* and flanking genes because of large deletions on chromosome 13q can also have developmental anomalies (eg, facial dysmorphia, congenital abnormalities, mental retardation, and motor impairment).[44,45] Children with large deletions including *RB1* have fewer tumours than do those with the common null mutations, perhaps because an unknown adjacent deleted gene is essential for tumour-cell survival.[46,47] Presumably, cells in which M1 and M2 mutations delete such an essential gene will die, and tumours would form only when M2 is a different mutation so that the cell has a normal copy of the essential gene.

Molecular genetic testing for *RB1* mutations has 95% sensitivity.[40] The risk that offspring will inherit the mutant *RB1* from the affected parent is 50%, which would result in a 97% risk of retinoblastoma and high lifelong risk of other cancers. The American Society for Clinical Oncology recommends that genetic testing be offered when family history suggests genetic susceptibility to cancer and when testing will affect management.[48] Screening for *RB1* mutations at any stage of pregnancy can be done once the familial *RB1* mutation is known (panel). Infants who carry their family's *RB1* mutation have such high risk of retinoblastoma that guidelines from the Canadian Retinoblastoma Society[19] recommend obstetrical care and premature delivery (at 36 weeks' gestation) to allow best possible early treatment of small tumours. Early detection of small-volume tumours and timely intervention with focal laser treatment and periocular topotecan often cures the disorder (figure 3), and the patient develops good vision with minimum morbidity.[49] Young relatives (offspring, siblings, and first cousins) who do not carry the family's mutation can avoid repeated invasive surveillance procedures under anaesthesia.[36,50] The M1 or M2 *RB1* mutations are also useful tumour biomarkers to detect any residual disease in cerebrospinal fluid and bone marrow before a supralethal-dosage chemotherapy regimen or autologous peripheral haemopoietic stem-cell transplant is used.[51]

Genetic testing for *RB1* is the standard of care in Canada and other countries,[19] but is not available in developing countries. Detection of the novel *RB1* mutation in a proband costs around US$3000. High-sensitivity molecular diagnosis substantially reduces health-care and family expenses and improves the quality of care.[36,50] Next-generation-sequencing technologies promise reduced costs because of high efficiency. A so-called global-to-local model of health service would directly connect forefront genomic science with local teams. Regional clinical laboratories would validate genomic results and test at-risk family members, and local health-care workers would use the knowledge to improve health care for probands and

their families. Local teams would gain scientific and clinical skills with access to global standards and validated technologies, participation in peer certification, and opportunities for regional, socially responsible entrepreneurship. This shift in genomic diagnostic clinical translation could become broadly relevant to health care.

Genetic progression of retinoblastoma

Although *RB1* loss means that a susceptible retinal cell can become malignant, it only produces retinoma, the benign precursor of retinoblastoma.[30,52] Retinoma is identified in 5% of individuals, either incidentally or because they have a child with retinoblastoma.[52] However, retinoma is also recorded in 16% of eyes enucleated because of retinoblastoma,[30] suggesting that it is a common precursor of retinoblastoma. Non-proliferative retinomas show loss of *RB1*, and low-level genomic instability—ie, extra copies of genes on chromosome 1q, including the motor protein, *KIF14*, and the regulator of apoptosis, *MDM4*.[30] Highly proliferative retinoblastomas show high-level genomic instability,[53] with increased copies of the oncogenes *KIF14*, *DEK*, *E2F3*, and *MYCN*, and loss of the tumour-suppressor gene *CDH11*.[54] What causes a benign retinoma to become a malignant retinoblastoma could be accumulation of genomic instability, or an as-yet unidentified event.[30] All cancers are associated with somatic mutations, and investigators

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Panel: One family's history of retinoblastoma

The father was born in 1968 and survived because both eyes with retinoblastoma were removed before he was 3 years old. His son was born in 1996, 10 days post-term. One eye was removed, but the tumours in his other eye were successfully treated with chemotherapy, focal laser treatment, and cryotherapy. The daughter was tested before her birth in 1999, because the precise germline null *RB1* mutation of her father and brother was known to be an 11 bp deletion on exon 14. She was electively delivered at 36 weeks' gestation, and her first tumour in the left eye (figure 3) was treated immediately with focal laser treatment only. All 12 tumours in her eyes were successfully treated with only focal laser treatment and cryotherapy, resulting in excellent vision in each eye.
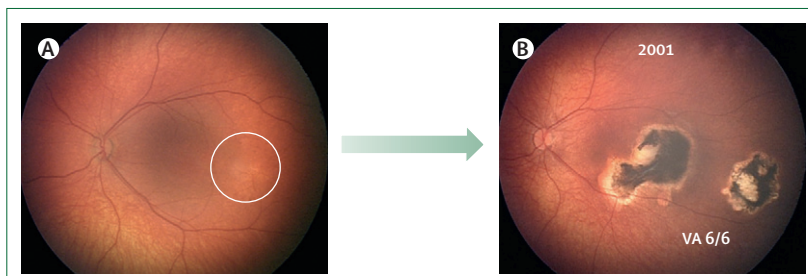

Figure 3: **Progression of retinoblastoma**
At 36 weeks' gestation (A), one small tumour was present in the left eye (white circle). Scars from laser treatments remain, sparing the fovea and vision (B).

are doing whole-genome sequencing of cancers to identify mutations that cause malignancy.[55] Such cancer genes could promote tumour growth, aggressiveness, resistance to therapy, and metastasis.

Medical management of retinoblastoma
Clinical classification
Classification of the extent of cancer at presentation is fundamental for assessment of prognosis, prediction of outcomes, initial treatment, and most importantly improvement of therapy through rigorously conducted clinical trials.[23] The first classification of intraocular retinoblastoma by Reese and Ellsworth[56] predicted the outcome of external-beam radiotherapy. When the high risk of secondary malignancy induced by radiation in children with constitutional *RB1* mutations was identified in the 1980s, chemotherapy replaced radiotherapy.[57,58] The International Intraocular Retinoblastoma Classification (IIRC) for prediction of outcomes for eyes treated with chemotherapy and focal laser treatment was accepted at the 2003 meeting of the International Society of Genetic Eye Disease and Retinoblastoma.[23]

A consistent clinical staging system is essential to enable communication and assess outcomes. However, ad-hoc changes in clinical criteria for each stage have made the IIRC inconsistent in some studies,[59,60] even within the Children's Oncology Group.[59] These discrepancies dangerously undermine the prognostic value of the IIRC, leading to both overtreatment and undertreatment. Patients' lives could be jeopardised if enucleation is delayed by attempts to cure eyes with high-risk features (eg, orbital cellulitis, hyphaema, media opacity, neovascular glaucoma, tumour anterior to the retina, suspicious optic nerve, or suspected extraocular disease on imaging), so that the tumour spreads extraocularly when prompt surgery would have cured the disease. Adverse features and microscopic extraocular spread of the tumour requiring intensive treatment can be accurately assessed only by histopathology of the high-risk eye.[59,60]

We recommend IIRC classification of each eye by extent of intraocular disease at diagnosis, and use of the seventh edition of the American Joint Committee on Cancer and International Union Against Cancer's staging (TNM clinical classification) to assess the whole patient by extent of extraocular disease.[22] TNM is the gold-standard classification to establish an appropriate care plan for patients with cancer. Because TNM is used worldwide (subject to regular revisions based on accumulated evidence) and is enforced by an international expert committee, ophthalmology journals now recommend use of the cTNM classification system for staging of retinoblastoma.[61]

Enucleation
A definitive cure for intraocular retinoblastoma is achieved by removal of the eye before the tumour spreads.[62] Prompt removal of high-risk eyes showing signs of potential tumour spread (eg, orbital cellulitis, poor view of the inside of the eye, bleeding inside the eye, neovascular glaucoma, tumour anterior to the retina, suspicious optic nerve, or suspected extraocular disease on imaging) will cure most children. The secondary goal to save vision of patients with bilateral retinoblastoma who would otherwise become blind— might necessitate chemotherapy with focal laser treatment and cryotherapy, or as a last resort radiotherapy. However, successful treatment of bilaterally affected children has meant that similar treatment has been given to unilaterally affected children instead of primary enucleation, who could die because of delays to removal of the high-risk eye.[62] Although unilateral cTNM cT1a or b (IIRC A and B) eyes could be saved with recovery of useful vision, to salvage a severely affected unilateral eye might not be in the best interest of a child with one normal eye.[18] Timely enucleation reduces risk of metastatic spread, morbidity, side-effects of chemotherapy and focal laser treatment, and repeated examinations under anaesthesia.

Care must be taken when eyes with intraocular retinoblastoma are enucleated, because the tumour could spread. Orbital implants are important for subsequent bone growth and a good cosmetic appearance. The myoconjunctival technique, in which the surgeon places a simple, inexpensive plastic (polymethyl methacrylate) implant posteriorly in the orbit, and attaches rectus muscles to the conjunctival fornices, results in excellent movement of the prosthesis, as shown in a randomised study.[63] Risk of orbital disease is not a reason to avoid an implant, because imaging and treatment of orbital recurrence can be treated without interference from the implant.

Some useful vision can be salvaged in eyes of some unilaterally affected children when tumours are small by expensive and invasive treatment. These therapies are not available in most countries of low and middle income. No child with unilateral intraocular disease should lose his or her chance of a cure, or die from metastases, because delayed removal of a severely affected eye allows extraocular spread.

Commonly, families reject enucleation as curative treatment because of perceived social stigma and poor understanding of the high quality of life after unilateral enucleation, or when they falsely believe that other treatments offered far from home might save the eye. With appropriate support, even children who lose both eyes to retinoblastoma can go on to lead full and highly productive lives.

Histopathology of enucleated eyes
Careful histopathological examination of enucleated eyes is essential to confirm or rule out metastatic spread (figure 4). Eyes are graded according to the pTNM pathology classification.[22] Detailed examination of pathological changes in the enucleated eye is crucial to
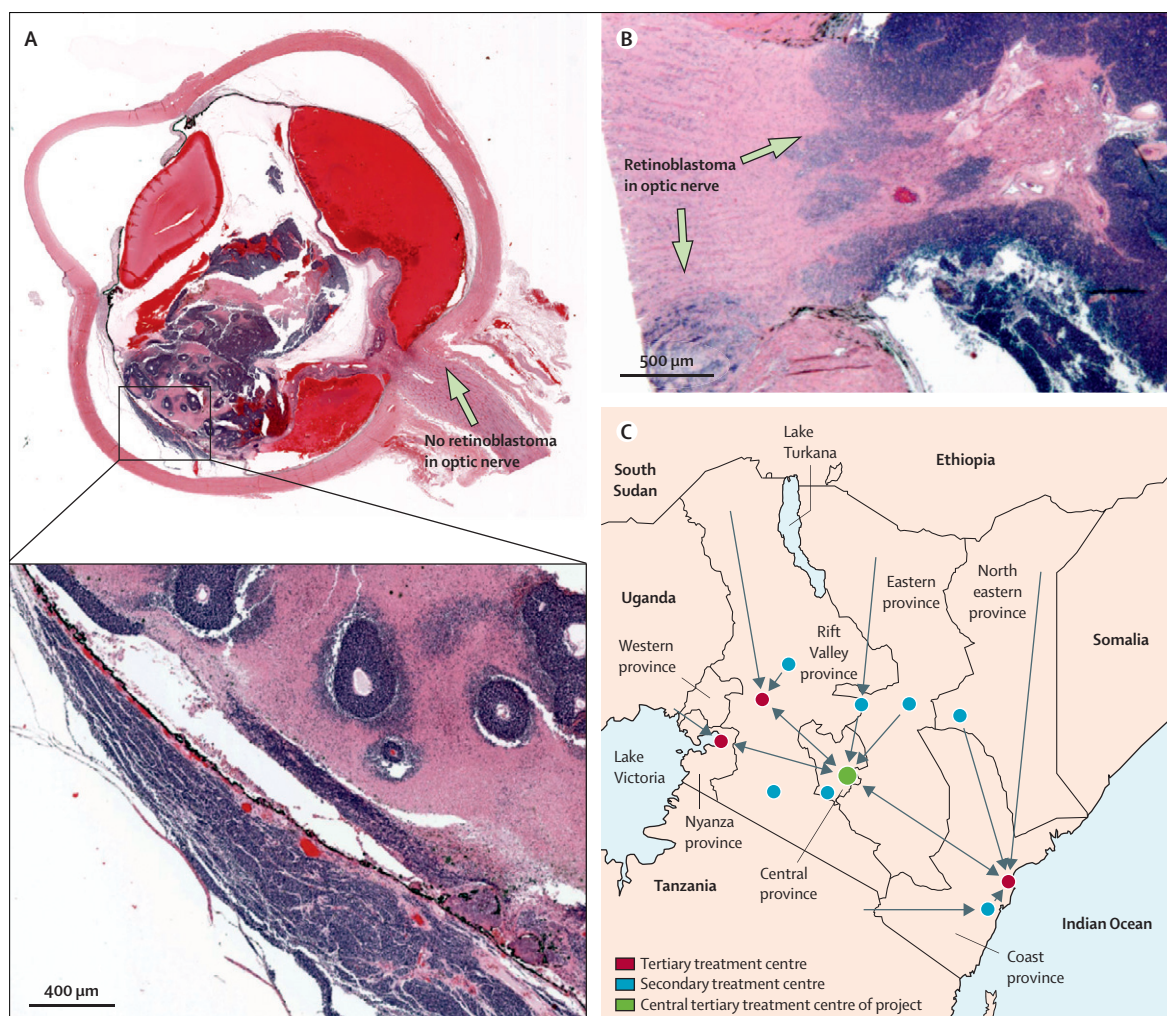
***Figure 4:* Histology of removed eyes and Kenyan collaborative project**
The features in the eye removed because of retinoblastoma that suggest risk of spread outside the eye include: (A) invasion of the choroid; and (B) tumour extension into the optic nerve. Microscopic slides can be scanned and viewed online, supporting multidisciplinary management irrespective of geography. For example, in the Kenyan RB Collaborative Laboratory project (C), patients are referred (arrows) to centres focusing on retinoblastoma, in which histology slides are prepared and scanned for shared management on the internet.

assess risk of tumour spread, and identifies whether adjuvant postoperative treatment or metastatic surveillance is necessary.[18] Late removal of clinical stage cT3 (IIRC E) eyes (ie, still clinically intraocular), because chemotherapy given before enucleation results in a false reduction or masking of the pathological staging, induces complacency about the risk of extraocular disease, and increases mortality.[62] When the optic nerve, choroid, or both are shown to be involved, curative adjuvant treatment and metastatic surveillance is recommended. By the time extraocular disease is clinically obvious, cure is very difficult.[64] When extraocular disease is already present at diagnosis, intensive treatment is necessary to attempt to save the child's life.

A worldwide issue is poor access to comprehensive retinoblastoma pathology. Long-delayed inaccurate pathology reports impede development of a rational management plan. In the absence of accurate pathology, doctors could discharge children perceived to be cured by surgery alone without follow-up surveillance, or proceed with unnecessary postoperative adjuvant chemotherapy in a well meaning, but misguided approach to the patient.

In Kenya, an experiment is under way to address this problem (figure 4).[26,27] The Retinoblastoma Collaborative Laboratory Service will receive specimens or sections of eyes and provide detailed reports based on standard operating procedures approved by the Kenyan National Retinoblastoma Strategy. Scanned slides will be reviewed on the internet, providing feedback to clinicians to support rational treatment decisions. This experiment will measure the effect of timely, accurate pathology reports on survival and quality of life.

For the **slides** see http://demo.aurorainteractive.com

Clinical trials

The guidelines from the Canadian Retinoblastoma Society[19] and an attempted meta-analysis[65] draw attention to the absence of class A evidence from randomised clinical trials to guide treatment. As a result, consensus recommendations and current practice at retinoblastoma centres are the basis for these guidelines. Clinical trials are the gold standard for evidence-based care, because they ascertain utility, efficacy, and safety of new methods. Because retinoblastoma is rare, few clinical trials have been completed. A search of ClinicalTrials.gov on Nov 12, 2011, yielded 57 results, of which 22 trials are investigating the efficacy of a treatment specifically targeted to patients with retinoblastoma (table 3). Only six are multicentre trials, with most participating centres in high-income countries. Middle-income countries are not widely represented (five of 19 studies), and no investigations are occurring in low-income countries. As shown in other paediatric cancers, rigorous multicentre trials led by multidisciplinary teams will most effectively improve care for all children with the disorder.

Systemic chemotherapy for intraocular retinoblastoma most commonly consists of carboplatin, etoposide, and vincristine.[67] The Toronto Protocol[58,67,68] combines short courses of high-dose chemotherapy and simultaneous, high-dose but short-duration ciclosporin to target multidrug resistance without incurring increased chemotoxicity. Short courses of chemotherapy reduce risk for short-term and long-term toxic effects. The Toronto Protocol is being studied in an international, multicentre clinical trial (NCT00110110; table 3). Even long-term systemic chemotherapy alone cannot be relied on to control intraocular retinoblastoma. The good initial responses must be consolidated with focal laser treatment or cryotherapy, or both.[67,69] Close surveillance with this treatment at frequent examinations under anaesthesia is necessary for 2 years or longer after chemotherapy to ensure ablation of all tumour cells and establish a cure.

External-beam radiotherapy was first used to treat retinoblastoma in the early 1950s.[70] Only 40 years later was it fully recognised that radiation greatly heightens lifelong risk of second cancers for a child with a constitutional *RB1* mutation.[37,68,71,72] Retrospective studies[37,68,71,72] have shown that irradiated retinoblastoma survivors develop secondary cancers as soon as 10 years after diagnosis, a risk that persists throughout life. If radiotherapy had been studied through a formal clinical trial with mandated long-term follow-up, this grave danger might have been recognised much sooner, and many deaths would have been prevented. Chemotherapy combined with focal laser treatment has replaced radiotherapy as primary treatment, mostly because of radiotherapy's long-term oncogenic effects in individuals with constitutional *RB1* mutations.

Stereotactic or conformal radiation[73]—given in ways that minimise dose to bone and soft tissues—is mainly used for the remaining eye after chemotherapy, focal laser treatment, and brachytherapy have all failed. These new methods reduce cosmetic deformities associated with radiotherapy in young children. However, the long-term oncogenic effects of stereotactic and conformal radiation will not be known for many years. Other potential long-term effects of stereotactic radiation on the endocrine system (such as growth hormone), eyes (tearing, cornea, lens, retina), skin, soft tissues, bone, and brain tissue are unknown. A formal clinical trial with mandatory long-term follow-up would be informative about oncogenic potential and other possible long-term side-effects.

As with radiotherapy, many treatments for retinoblastoma have been adopted without evidence of effectiveness, complications, outcomes, or cost. Clinical trials are now starting that have rigorous eligibility criteria, predefined outcome measures, exclusion criteria, and assessment of adverse events. For example, few efficacy data are available for local periocular carboplatin,[74] but orbital morbidity has already been reported.[75,76] A phase 1 study[66] of an achievable dose of periocular topotecan (NCT00460876; table 3) in patients with relapsed or resistant bilateral retinoblastoma showed low systemic toxicity, but did not establish tumour responses.

Intra-arterial chemotherapy was used to treat retinoblastoma in 187 patients in Japan between 1988 and 2001.[77] However, the investigators initially described only technical success, without efficacy or toxicity data. Some follow-up data were reported in October, 2011.[78] Ophthalmic arterial infusion of melphalan is technically feasible and can result in striking regression of tumour.[79–81] These optimistic reports do not specify eligibility criteria, control of retinoblastoma, vision achieved, or survival rates of the eye or patient. Three single-institution studies could provide these important data (NCT01151748, NCT00906113, and NCT00857519; table 3). Meanwhile, as with the worldwide adoption of radiotherapy in the 1950s, intra-arterial chemotherapy is being widely used outside of formal studies.[82,83]

Disseminated leptomeningeal disease is the most difficult type of extraocular retinoblastoma to cure. The craniospinal radiation doses and volumes necessary for adequate treatment of leptomeningeal retinoblastoma are too toxic for young children. Radiotherapy causes growth, intellectual, cognitive, and endocrine comorbidities, particularly in children younger than 3 years.[84] Bone marrow, other metastatic sites, and disease in the cerebrospinal fluid might be cured with: systemic chemotherapy (with intraventricular chemotherapy for disease of the cerebrospinal fluid); complete surgical excision of accessible metastatic disease; or autologous peripheral haemopoietic stem-cell rescue of the marrow after supralethal-dose chemotherapy, with[85,86] or without[64] orbital and metastatic-site radiotherapy. These treatments are rarely available in developing countries.

Cure of trilateral disease, especially with leptomeningeal spread, is also rare, but is possible.[87–89] When diagnosis of trilateral retinoblastoma can be made on the basis of retinal findings and CT or MRI of intracranial disease,

	Phase	Study group	Treatment	Date first registered	Primary sponsor	Subsites	Date completed
Completed							
NCT00002675	2	Patients with retinoblastoma	Carboplatin, etoposide, and vincristine; cisplatin; cyclophosphamide	May, 1995	NY, USA	No	Jan, 2001
NCT00002794	2	Intraocular bilateral or multifocal unilateral retinoblastoma	Carboplatin and vincristine	Feb, 1996	TN, USA	No	Oct 3, 2011
NCT00004006	2	Extrachoroidal or metastatic retinoblastoma, or both	Carboplatin and etoposide; cyclophosphamide; topotecan; doxorubicin; radiotherapy; ABMT	Nov 1, 1997	TN, USA	No	Oct 1, 2011
NCT00079417	3	IIRC group B eyes	Neoadjuvant carboplatin/vincristine; FT, with or without brachytherapy	Dec, 2005	NCI/COG	USA	Jan, 2010
NCT00901238	1/2	Advanced unilateral or bilateral retinoblastoma	Intra-arterial melphalan	May 1, 2006	NY, USA	No	Jul 1, 2009
NCT00460876[66]	1	Relapsed bilateral retinoblastoma	Periocular topotecan	March, 2007	Argentina	No	April, 2008
Active, not yet recruiting							
NCT00073384	3	Intraocular retinoblastoma	Carboplatin, etoposide, and vincristine; subtenon carboplatin; FT	Nov 4, 2003	NCI/COG	USA	..
NCT00360750	..	Advanced enucleated retinoblastoma	Carboplatin, etoposide, and vincristine; cytarabine, with or without radiotherapy	Sept, 2005	CCLG	UK	..
NCT00179920	2	Intraocular germline retinoblastoma	Carboplatin; etoposide; FT	Sept 12, 2005	IL, USA	No	..
NCT00186888	3	Intraocular retinoblastoma	Individualised treatment*	Sept 12, 2005	TN, USA	No	..
NCT00335738	3	Enucleated retinoblastoma	Carboplatin, etoposide, and vincristine for high-risk disease; observation for no risk	Dec, 2005	NCI/COG	USA, Canada, Australia, India, New Zealand	..
Recruiting							
NCT00110110	2	Bilateral IIRC group B, C, or D eyes	Carboplatin, etoposide, and vincristine; CSA; FT (Toronto Protocol)	June, 2004	ON, Canada	Canada, Singapore, India, Chile	..
NCT00432445	2	Intraocular and periocular retinoblastoma	PBR	Feb 5, 2007	TX, USA	No	..
NCT00554788	3	Extraocular retinoblastoma	Carboplatin, etoposide, and vincristine; thiotepa, cisplatin, cyclophosphamide, radiotherapy, ASCT	Feb, 2008	NCI/COG	USA, Canada, Australia, Argentina, Egypt, India†	..
NCT00857519	..	Advanced unilateral/bilateral retinoblastoma	Intra-arterial melphalan; intra-arterial carboplatin	Jan, 2009	PN, USA	No	..
NCT00889018	..	IIRC group C and D eyes	Comparison of two different doses of subtenon carboplatin	April 27, 2009	Delhi, India	No	..
NCT00906113	1/2	Patients with retinoblastoma	Intra-arterial melphalan	May 19, 2009	Israel	No	..
NCT00980551		Bilateral retinoblastoma	Vincristine and topotecan; subconjunctival carboplatin	Sept 18, 2009	OH, USA	No	..
NCT01393769	2	Unilateral IIRC group D eyes	Intra-arterial melphalan	Nov 1, 2009	Spain	No	..
NCT01293539	2	Intraocular retinoblastoma	Intra-arterial melphalan	March 1, 2011	MD, USA	No	..
NCT01466855	..	Intraocular retinoblastoma	Intra-arterial melphalan	Oct 19, 2011	OH, USA	No	..
Not yet recruiting							
NCT01151748	2	IIRC group D and E eyes	Intra-arterial chemotherapy	Sept, 2010	CA, USA	No	..

ABMT=autologous bone-marrow transplant. IIRC=International Intraocular Retinoblastoma Classification. FT=focal laser treatment. NCI= National Cancer Institute. COG=Children's Oncology Group. CCLG=Children's Cancer and Leukemia Group. CSA=ciclosporin A. PBR=proton-beam radiation. ASCT=autologous stem-cell transplant. *Including: enucleation; vincristine and carboplatin; FT; external-beam radiotherapy; vincristine and topotecan; vincristine, carboplatin, and etoposide; vincristine, cyclophosphamide, and doxorubicin; and periocular carboplatin. †These subsites were not listed on the database, but were reported as subsited by the trial principal investigator.

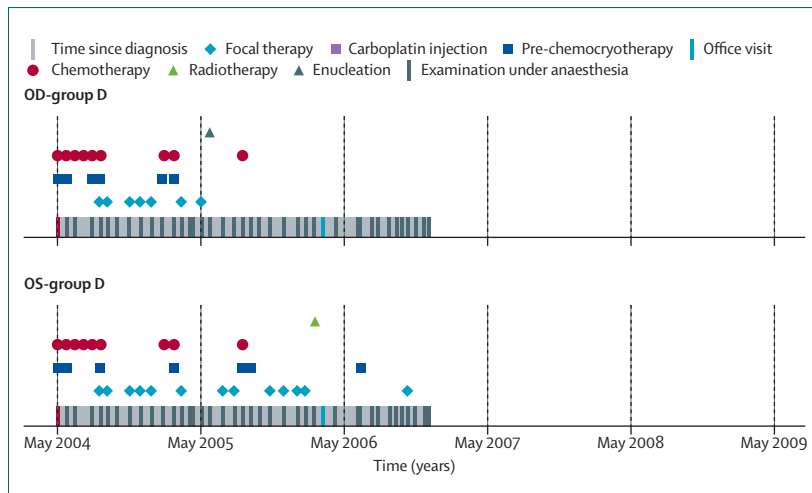*Table 3*: Clinical trials of retinoblastoma treatment listed on ClinicalTrials.gov grouped by status

Figure 5: eCancerCare database

The disease-specific electronic patient illustrated clinical timeline (DePICT) displays all treatments since diagnosis of retinoblastoma. Point-of-care data entry, digital drawings, images of tumours, and details of events can be viewed online in the database, within the health institution or in a national database.

biopsy of the intracranial tumour should be avoided because it might jeopardise the chance of cure.[90]

In view of the reality that many children in countries of low and middle income worldwide die of retinoblastoma, palliative-care protocols are urgently needed. Chemotherapy provides good palliation of gross orbital disease. Radiotherapy could provide symptomatic relief.[91] Until extraocular disease can be substantially reduced worldwide by early diagnosis and treatment, clinical studies are also necessary to optimise palliation. Extraocular retinoblastoma is rarely recorded in high-income countries, but is very common in countries of low and middle income (table 1).

Follow-up

Follow-up is defined as the period after the last active disease is detected. During short-term follow-up, the child is monitored for recurrence of primary retinoblastoma; in long-term follow-up, all patients with heritable *RB1* mutations, or who have undergone chemotherapy, external-beam radiotherapy, or autologous peripheral haemopoietic stem-cell transplant are monitored for second primary tumours.[19] Long-term side-effects of chemotherapy with autologous peripheral haemopoietic stem-cell transplant, including risk of second cancers, are not well documented. Meta-analyses are not informative because every child is essentially treated ad hoc. The rate of second malignancies in retinoblastoma survivors with low penetrance or mosaic *RB1* mutations is unknown, but is presumed to be lower than that in those with constitutional null *RB1* alleles.

Family support

Support programmes provide assistance and help families to cope with the many stresses associated with retinoblastoma. Abandonment of therapy is the main cause of treatment failure in curable children in countries of low and middle income, apparently because of limited resources and a perceived stigma of cancer or loss of an eye. The emerging online networks of families who assist each other to cope and locate essential services and resources might improve the situation. Families in countries of low and middle income could, however, remain isolated from such support.

Because families in these countries increasingly learn about eye-salvage treatments in high-income countries, they might seek alternatives to enucleation. For all children, treatment as close to home as possible is the best approach. Delays and poor follow-up associated with attempts to seek care internationally too often result in preventable death. The financial and psychological burdens of international care affect families for many years after treatment. An honest, realistic approach to the child's whole wellbeing, including liaison with the local medical team, could best achieve appropriate care and the child's best chance of survival with good quality of life.

Complexity of care

Retinoblastoma is best managed by a multidisciplinary team, including but not limited to ophthalmologists, oncologists, paediatric nurses, imaging specialists, pathologists, pharmacists, child-life specialists, and social workers.[19] An electronic medical-record system designed specifically to capture data relevant to retinoblastoma could help to manage the complexity of care. eCancerCare is a point-of-care medical-record database based on consensus practice guidelines, which summarises medical history in visual timelines (figure 5).[92] The system allows continued professional development of the multidisciplinary team, improves communication, and promotes adherence to care guidelines and research. The graphical timelines make treatment and outcomes easy to understand for both health-care workers and parents, irrespective of language and education.[92]

Conclusions

A worldwide network dedicated to children and families affected by retinoblastoma is emerging. The internet will help in many ways: parent-to-parent support can be established, shared care can be assisted by the eCancerCare database and digital pathology, and multicentre clinical trials could obtain class A evidence for care. Internet communications are changing the care for children with retinoblastoma, and allow clinicians to aspire to equal access to evidence-based care for all children with retinoblastoma.

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