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Retinoblastoma: Identifying the Diagnostic Signs for Early Treatment

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Abstract

Retinoblastoma is a rare but significant cause of childhood eye cancer world-wide. The prognosis depends upon early diagnosis and treatment but also upon accurate classification of the tumours. Unilateral incidence is normally non-hereditary compared with bilateral incidence where secondary tumours are more common. Survivorship is much better for unilateral compared with bilateral and trilateral retinoblastoma. Early signs are important to detect and photography can assist in identifying no return of "red-eye" during flash photography and yellow appearance of the tumour. Treatment options are discussed together with new psycho-oncology approaches that address potential trauma in the survivor as well as in the family of the survivor.

Keywords: Childhood cancer; Diagnosis; Eye cancer; Prognosis; Rehabilitation; Retinoblastoma; Treatment

Introduction

The human eye is a complex organ that allows immense detail to be assimilated and, with both eyes, enables judgement of depth via stereoscopic vision. Sometimes, poor vision is overlooked, especially in children, when the ability to express difficulty is limited, or when the effects of poor vision are subtle. In particular, Retinoblastoma (Rb) is a rare type of eye cancer but the most common intraocular malignancy of early childhood [1-3], forming 3 per cent of all childhood cancers [4]. It is an aggressive disease that evolves as a tumour of the retina, the thin layer of cells on the inside at the back of the eye [5].

Although almost exclusively a cancer of childhood, it has been detected in the foetus and can also occur in older children [6]. Rb presents from birth to 5 years of age, typically being diagnosed in children before the age of 3 years of age [7, 8]. In terms of prevalence, it is equal in regard to age, sex, and right or left eye [9].

In the UK, it affects between 40 - 50 children every year [10] and occurs because of errors or mutations to a gene we all possess called the RB1 gene [1]. Reports of small sample cohorts from the Netherlands show that relative risks following in-vitro fertilisation are significantly raised, though the possible association in population-based studies is yet to be established [11].

Data for the period of 2006-2010 show a five-year survival rate of 100 per cent, in the UK [10]. Survival rate in developed countries averages at 95 per cent compared to 50 per cent worldwide [8, 11]. Delay in presentation, diagnosis and access to resources are the most common explanations for this difference [12].

Genetic inheritance

We inherit two copies of the RB1 gene, one from each parent. If both copies of this gene are damaged in a single cell, followed by a chance mutation in the child's retinal cells, then one of the important "brakes" or "stops" of cell growth and cell division is lost giving rise to tumours in the retina. During the early stages of eye development, retinoblasts (cells) divide into new cells and fill the retina. At a certain point the cells stop dividing and develop into mature retina cells that detect light. In rare cases retinoblasts continue to divide and grow out of control forming Rb [14].The RB1 gene is located on chromosome 13, position 14.2 and is a tumour suppressor gene [3]. Each cell normally has two RB1 genes. As long as a retinal cell has one working RB1 gene, it will not form Rb. However, when both Rb1 genes are mutated or lost, gene changes occur which may cause cells to become cancerous.

Genetically, there are four possibilities: firstly, if the mutated gene is present in the parent with the disease or if the parent is a carrier of the disease, and if the child's retina mutates, then tumours typically occur bilaterally [15] and with a high risk to the brothers and sisters and future children also having the bilateral disease. There are treatment options in these cases but often the child loses substantial sight in one or both eyes and if the tumour is aggressive and large then the eye is also lost and necessitates a surgical implant.

The second genetic scenario is when the RB1 gene has not mutated within the parent but instead it mutates in either the egg or sperm. This gives rise to Rb if the child's retinal cells also mutate. Thirdly, mutation of the RB1 gene may occur during early embryonic development before the cells are defined and if mutation occurs in the retina of the unborn child then Rb can occur unilaterally or bilaterally with lower risk to brothers and sisters and to future children.

Lastly, if the gene mutates in the retina of the healthy child, then Rb often occurs unilaterally with a low risk for brothers and sisters and future children. There is a risk in all scenarios of secondary cancers occurring later in life to soft tissue areas and to bone. There has been a step away from classifying using "genetic" and "non-genetic" terminology since theoretically, all scenarios are "genetic", i.e. involve mutation of the RB1 gene.

The genetic possibilities are "heritable" versus "non-heritable" though "mosaic" has been used when the picture may be less definitive and if some but not all cells carry the mutated gene but only one eye has appeared with Rb tumours.

It is estimated that 40 per cent of children with Rb have a germ-line mutation in one RB1 gene, thus all the cells in the body have a defective RB1 gene [6,16]. In 25 per cent of these cases, the child has inherited it from one of their parents. The remaining 75 per cent is the result of a mutation developed after conception while in the womb [15]. Hereditary Rb is diagnosed on average at one year of age and the child is more likely to have multifocal and bilateral disease [15]. Having the genetic form of the disease also increases the child's risk of developing secondary primary cancers.

The most common secondary primary tumours are osteosarcomas, brain tumours and soft-tissue sarcoma [16]. Fontela et al. [17] reported that patients with bilateral disease are at a 5 per cent chance of developing another cancer during the first 10 years of follow-up, 18 per cent within the first 20 years and 26 per cent within the first 30 years. This makes secondary primary tumours the greatest cause of death for patients with Rb [6].

If a child has the hereditary form of Rb, yet they do not have an affected parent (as the mutation happened in the womb), the chance that the parents will conceive another child with Rb is less than 5 per cent. However, the patient with hereditary Rb has a 50 per cent chance of passing the abnormal gene onto their offspring [15] which is why this form of Rb is called hereditary.

The remaining 60 per cent of children with Rb do not have the Rb1 gene mutation in all cells of the body. Instead, the Rb1 mutation occurs early in life in a single retinal cell by chance, sometime after conception [4]. As of yet, it is not known how or why this occurs [18]. Patients with non-hereditary Rb have unilateral, unifocal disease [8] with the average age at diagnosis being two years of age and the disease is not passed to the patient's offspring.

The disparity in age of onset and tumour number and location between the hereditary and non-hereditary form of Rb supports Knudson et al. [15] 'two hit' hypothesis [3]. If a patient with unilateral or bilateral Rb has relatives with the disease, it can be assumed that the patient has the inherited form of Rb. However, it cannot be assumed that a patient without a family history of the disease has the non-hereditary form. In other words, whilst all bilateral cases are hereditary, not all unilateral cases are non-hereditary. 10 per cent of patients with unilateral disease have underlying germline mutation and are at risk of developing the disease in the uninvolved eye [4]. It is therefore necessary to have all patients with Rb genetically tested to determine whether the Rb is (non) hereditary [7].

The current techniques that are used can detect 90 per cent of mutations in patients with bilateral Rb and 85 per cent in patients with unilateral Rb and in contrast, 87 per cent of unilateral Rb is caused by post-zygotic mutation occurring at the early stages of embryo development that can lead to mosaicism [19].

Trilateral Rb occurs in 5 per cent to 15 per cent of patients with heritable Rb: usually bilateral but can also be unilateral [20]. Trilateral Rb results from the development of an independent brain tumour that forms in the pineal gland. Trilateral Rb is relatively uncommon, does not result from the spread of intraocular Rb and is usually fatal. The condition is usually diagnosed 2 years following diagnosis of Rb and has a median survival time from diagnosis of the disease of 9 months.

Given the poor prognosis and the short interval between diagnosis of Rb and the occurrence of trilateral disease, imaging tests are recommend every 6 months for five years for those with the hereditary disease or unilateral disease and a positive family history [20].

Diagnosis

Early diagnosis is essential if the tumours are to be detected and treated and if the spread of tumour is to be stopped. Often parents may see an unusual colour in the eye or eyes of their children when photographed such as a yellow colouring (a little similar to a cod liver oil capsule) or a white colour (Figure 1) [13] rather than the natural red pigment of the retina [1]. Flash photography using the installed camera of a modern mobile phone (commonly, backside-illuminated 5 megapixel, or greater, rear-facing camera, with 3.85 mm f/2.8 lens) is ideal for detecting the normal "red eye" that should be reflected from the retina. Author 1, suggests that, anecdotally, close-up flash photography in this manner is helpful and often re-assuring as initial screening but parents are advised to seek professional confirmation if there is any doubt about these signs especially since early detection of Rb is of paramount importance.

Figure 1: Yellow colour depicting typical eye tumour compared with normal red of retina [13]

Associated signs such as a strabismus (squint) or head-turning in compensation for poor sight, may also be noticed in a child with Rb. Curiously, some children who have lost one of their senses or who have lost one of their sense organs early in life may compensate for the loss; and reports indicate that there is often normal cognitive development [21]. Compensation can occur by having "super-functioning" in the remaining functional eye. It would seem that losing the sight (and often the eye) before the age of one years' old may result in functioning of the remaining healthy eye to be better than average in terms of sight and visual functioning acuity. It has also been seen in those who have lost other senses such as hearing or who have lost sight completely and have developed acute hearing, touch, or taste senses instead [21]. It is as if additional meaning is gained in the remaining sensory mechanisms. As the famous philosopher and writer, Thomas Carlisle wrote, "… indeed it is well said. In every object there is inexhaustible meaning. The eye sees in it what the eye brings means of seeing." [22].

The prognostic outcome of life and vision in patients with Rb has significantly improved in recent years. Factors such as improved methods for diagnosis and treatment, and age and stage of tumour(s) as well as type of Rb, have a contributing role. Patients diagnosed before the age of two are thought to have a higher survival rate than those diagnosed at two years or older. Reasons for this include advanced presentation and an increased risk of extra-ocular extension and metastasis in those who are diagnosed at a later age [23]. Consequently, more intensive treatment is required which may adversely affect vision and survival of the patient.

Patients with intraocular Rb have a five-year survival rate of 98 per cent compared to 10 per cent in patients with extra-ocular Rb. Furthermore, patients with the hereditary from of Rb have a higher risk of developing secondary primary cancers and are susceptible to the development of trilateral Rb [20]. Those with trilateral Rb have an average survival rate of eight months when treated compared to one month in those untreated.

Clinical manifestations of Rb vary dependent on the stage of the disease [4,9]. The most common presenting sign at 60 per cent is leukocoria [6]. When a bright light is shone into an eye, blood vessels will reflect a red colour back. In those with Rb the pupil will appear white or yellow. This is also known as 'Cat's eye' and is often noticeable when a photograph is taken using the flash [8]. As a late manifestation of Rb, the tumours are likely to be large. However prognosis remains high at 88 per cent of the five-year survival rate [6].

The second most common sign at 20 per cent is strabismus. As an early sign, prognosis and eye salvage is high. Strabismus (misalignment of the eye) results from a loss of central vision in one or both eyes [7]. It involves a lack of coordination between the extraocular muscles preventing the gaze of each eye at the same point. Thus, one eye may look straight ahead, upward, downward or outward. Other presenting symptoms include reddish pupil, larger than normal pupil, poor or decreased vision, wandering eyes (nystagmus) and parental history of Rb [23].

If Rb is suspected, a red reflux test needs to be conducted [9]. This test is used to view both reflexes at the same time in order to determine if the patient has normal ocular alignment. The test is conducted in a dimly lit or dark room using an ophthalmoscope at 50 cm away from the child. This allows simultaneous illumination of both eyes making it easier to compare the reflex. Pupillary dilation has been found to be helpful when performing this test. To be considered normal, a red reflux will be systematic and shown in both eyes. Dark spots in the red reflux, a diminished reflux and the presence of a white reflux indicate an abnormality [1]. Thus, an urgent referral to an ophthalmologist for further evaluation is required [24,25]. It is advised that children with a positive family history of Rb are screened soon after birth. This needs to be repeated every four to six weeks up to the age of one year and then every two to three months until three years of age [25].

Once Rb has been diagnosed, imaging tests are conducted to find out if the cancer has spread within or beyond the eye. This process is known as staging. Staging not only depicts how far the cancer has spread, it also provides prognosis of survival, outlook for saving vision, size and location of the tumour(s) and likelihood that certain treatments will be effective [3]. Imaging tests used in the detection and diagnosis of Rb are ultrasound, Magnetic Resonance Imaging and Computerised Tomography scan [26].

Diagnostic tools

An ultrasound (echography) examination helps determine the thickness or height of the tumour [26]. Whereas most children with Rb will have one Magnetic Resonance Imaging scan [8] that provides detailed images of the eye and surrounding areas such as the spinal cord and brain, those with bilateral Rb may have scans for several years after treatment to ensure no further spread. The procedure in children often requires a general anaesthetic to achieve complete stillness in the patient.

Computerised Tomography scan, often with contrast medium dye, is helpful for detailed cross-sectional images [7], particularly to determine the size of the Rb tumour and its spread within the eye and to nearby areas. Despite the effects of radiation, calcification is detected better using this test and is particularly helpful when the diagnosis of Rb is not clear.

In cases where there is a strong reason to think that Rb has spread to the skull or other bones, a bone scan is undertaken. However, it is important to be aware that the areas may be a result of other bone changes [18]. Other types of tests that are carried out when there are additional symptoms (weight loss, vomiting), or abnormal findings associated with the diagnosis of Rb include blood tests (particularly, for liver and kidney functioning and changes in chromosome 13), lumbar puncture and bone marrow aspiration and biopsy.

Differential Diagnosis

Due to a number of ocular disorders in children clinically resembling Rb, it is important that the diagnosis of Rb is fully confirmed prior to the start of treatment. Shields and colleagues [27] found that 42 per cent of patients who were referred with possible Rb had lesions that simulated Rb. In this study a total of 23 different conditions were accounted for the pseudo-retinoblastoma including persistent hyperplastic vitreous (blurred vision due to scarred vitreous), Coats disease (abnormal development of blood vessels behind the retina) and presumed ocular toxocariasis (rare infection caused by roundworms). Patients with these diseases often present with leukocoria - the most common presentation in Rb. Other less common conditions that may mimic Rb are congenital cataract, retinopathy of prematurity, Norrie disease and familial exudative vitreoretinopathy [28]. A careful clinical examination using the red reflux test as described above is usually sufficient to determine the correct diagnosis.

Staging

Rb is staged on the results of eye exams, imaging tests and in rare cases, biopsies. The stage of Rb determines best treatment option and can help predict a patient's prognosis. Rb is staged on the basis of whether it is intraocular, extra-ocular or recurrent.

Intraocular Rb is the earliest stage of the disease where the cancer is still within the eye. It may be confined to the retina or extend to other structures such as the optic disk, choroid or anterior chamber, however, does not extend beyond the eye. If left untreated for 12 months, metastasis is likely to occur and can become fatal within a few years [9].

Extra-ocular Rb is an advanced stage of disease where the cancer has spread outside of the eye. In these cases cells break away from the main tumour on the retina and float through the vitreous to reach other parts of the eye [18]. The cancer can spread either to the tissues

around the eye (orbital Rb), the central nervous system (CNS) or to the bone marrow or lymph nodes (metastatic Rb).

In the majority of cases, extra-ocular Rb occurs in developing countries due to late detection, limited access to resources and thus delayed diagnosis [28]. Recurrent Rb is where the tumour has recurred or progressed following initial treatment. The recurrent tumour may be confined to the eye, tissues surrounding the eye or other parts of the body.

In the UK, Rb is primarily detected and diagnosed before it has spread outside of the eye. Therefore, staging systems that apply only to intraocular Rb are used most often in this country. There are two main staging systems for intraocular Rb: the Reese-Ellsworth staging system, and the International Classification for Intraocular Rb. In the 1960s the Reese-Ellsworth classification was created based on intraocular tumour staging and globe savage after external beam radiotherapy (EBRT) [6]. The system divides eyes into 5 groups (I to V) and 10 subgroups ('a' and 'b' for each group) according to location, focus and the size of the tumours. Group I have the lowest risk of treatment failure and group V has the highest risk of enucleation. Tumour control for group I – III was reported to be 78 per cent compared to 20 per cent in group III-V [29].

During this era EBRT was the treatment modality of choice, however it had little success with multifocal and large tumours due to technical difficulty [29]. Consequently, these tumours were presumed more aggressive and were given a higher ranking in the classification system, implying a worse ocular prognosis [26].

With radiation being linked to disfigurement and increasing the risk of developing secondary cancers, particularly in those with hereditary Rb, chemo-reduction combined with focal treatments became the primary treatment modality [30]. This shift in treatment modality found that multifocal and large tumours do not have a worse prognosis than small, solitary macular tumours.

What emerged as the difficulty in treating Rb was the management of vitreous and sub-retinal seeds. By not addressing seeding, the Reese-Ellsworth classification was found to be a poor predictor of chemo-reduction success [31]. This led to the International Classification of Rb (ICRB) being developed in 2003, which is predominately based on the extent of sub-retinal and vitreous seeding with minor consideration of tumour size and location [29].

The International Classification of Rb (2003) is a staging system that divides intraocular Rb into 5 groups labelled A to E (Table 1). It is based on the natural history of Rb (early stage, group A to late stage group E) and on the likelihood of saving the eye following primary treatment of chemotherapy and adjuvant focal therapy [29]. Each eye is staged independently and the tumour with the higher grade is used to classify the eye.

GROUP	TUMOUR
A	Confined to retina; away from visual structures such as optic disk; < 3mm across.
B	Close to visual structures; > 3mm across.
C	Well-defined; small seeding.
D	Large; Widespread seeding.
E	Extensive; destruction of eye.

Table 1: The International Classification of Retinoblastoma

In group A and B the tumour remains confined to the retina. Group A tumours are less than 3 mm across and away from visual structures such as the optic disk whereas group B tumours are more than 3 mm and close to the visual structures. In group C and D, the tumours have spread into the sub-retinal and vitreous cavity. Group C indicates well defined tumours with small seeding compared to group D where there is widespread seeding and large tumours. Group E refers to extensive tumours that have destroyed the eye. Group A has the lowest risk of treatment failure whereas group E eyes are rarely salvageable, requiring additional EBRT or enucleation [32]. The chance of retaining useful vision decreases from group A to E [29].

Several classification systems have been developed for extra-ocular Rb, and some for both intraocular and extra-ocular Rb. Extra-ocular staging applies to cancer that has spread outside of the eye and takes into account the degree of local extension, intracranial metastasis and haematological metastasis. The International Rb Staging System (IRSS) encompasses both intraocular and extra-ocular Rb (Table 2). The IRSS is based on the extent of the disease [8]. The staging system is split into 5 sections ranging from stage 0 to stage IV. Stage 0 refers to intraocular cancer, thus patients with this stage of disease should be classified based on the International Classification System.

STAGE	STATUS
0	Intraoccular – refer to International Classification of Retinoblastoma.
I	Enucleation; some microscopic spread to optic nerve.
II	Spread to optic nerve and sclera.
IIIa	Spread to eye socket tissues.
IIIb	Spread to lymph nodes near to ear and/or neck.
IVa	Spread to blood; one or more tumours.
IVb	Spread to brain and/or spinal cord.

Table 2: International Retinoblastoma Staging System

Stage I refers to eyes that have been enucleated and there is some microscopic spread to the optic nerve. Stage II refers to tumour spread to the sclera as well as the optic nerve. Stage III is divided into two sub-stages: llla where the cancer has spread to tissues around the eye socket and lllb where the cancer has spread to lymph nodes near the ear or in the neck. Stage IV is also divided into two sub-stages: IVa where the cancer has spread to the blood where there are one or more tumours. IVb refers to cancer that has spread to the brain or spinal cord.

The TMN classification is particularly useful in describing the extent of Rb. It takes into account the size of the primary tumour and how far it has grown within and outside of the eye; whether or not the cancer has reached the lymph nodes and whether it has metastasised to other sites such as the bone marrow and brain [18].

Recurrent Rb

Recurrent Rb is cancer that has returned or continues to grow after treatment. The cancer may come back in the same place (local recurrence), nearby (regional recurrence), or in another place, (distant recurrence). Further testing is undertaken in order to restage the cancer. The cancer is re-staged depending on whether it is intraocular or extra-ocular. Intraocular and extra-ocular recurrences have very different prognoses and are treated in distinctly different ways.

Treatment Options

The goals of treatment for a patient with Rb are to save the patient's life, to save at least one eye and to prevent vision loss [18]. The management of Rb needs a multidisciplinary team approach including an oculist, paediatric oncologist, geneticist and an ophthalmic oncologist [32].

Treatment of Rb is highly individualised and is dependent on whether the cancer is intraocular or extra-ocular, unilateral or bilateral and unifocal or multifocal. Additional features that affect treatment choice include the age of the child, family and societal perception, overall prognosis, cost effectiveness of treatment and the size, location and number of tumours [32]. Treatment of Rb in the UK is primarily based on intraocular disease due to its high percentage at diagnosis.

There are several methods to manage intraocular Rb including focal therapy (photocoagulation, thermotherapy, cryotherapy and brachytherapy), local therapy (external beam radiation and enucleation), and systemic therapy (chemotherapy). While primary focal therapy treats small tumours, local and systemic therapy treats advanced tumours [32]. Combinations of treatments may be required to achieve tumour control [30].

Intraoccular Rb

Focal therapy: Focal therapy refers to a group of treatments that are applied directly to the eye. Focal therapy is performed under general anaesthetic and is repeated numerous times until all remaining signs of active tumour has disappeared [33]. A noticeable side effect of focal therapy is scarring of the retina thus affecting vision.

There are four main types of focal therapy used to treat Rb: photocoagulation, thermotherapy, cryotherapy and brachytherapy. Focal therapy is generally used to treat small to medium tumours that fall into group A-C on the International Classification for Intraocular Retinoblastoma and groups I to IV on the Reese Ellsworth Classification for Intraocular Retinoblastoma.

Photocoagulation therapy: Photocoagulation, also known as laser therapy, is used for small tumours, measuring less than 3.5 mm in thickness, residual tumour after chemotherapy and recurrence after chemotherapy [3]. Photocoagulation uses heat in the form of a laser to physically destroy tumour cells. The laser is directed to the affected areas of the retina through the pupil. Pharmaceutical drops are used to dilate the pupil. The heat of the laser cauterizes the blood vessels that surround and supply the tumours [9].

On average, photocoagulation is delivered 2 or 3 times with a month between treatments [11]. Photocoagulation is a painless procedure although the eye may be red following treatment. In rare cases photocoagulation can damage the retina, which can lead to blind spots or temporary retinal detachment.

Thermotherapy: Thermotherapy is recommended for small tumours, measuring 4 mm in diameter and 2 mm in thickness, close to the fovea or optic nerve, where other therapies might create greater visual loss [9]. Thermotherapy involves the use of heat to help shrink tumour cells. The heat often used in treating Rb is infrared rays and is directed either on the whole eye or localised to the tumour area [11].

The tumour is heated at a temperature between 40 and 60 degree Celsius until it turns a subtle grey, in order not to damage the retinal vessels [30]. Complete tumour regression can be achieved in 85 per cent of tumours using 3 to 4 sessions. Common complications include retinal detachment, clouding of the lens, shrinking off the iris and damage to the retina [30].

Cryotherapy: Cryotherapy is primarily used to treat small tumours, measuring up to 4 mm in diameter and 2 mm in thickness, located on the front part of the retina [11]. Cryotherapy uses liquid nitrogen to destroy the Rb cells by freezing them [9]. A small metal probe is placed on the outer surface of the eyeball next to the tumour, which is frozen and thawed several times.

The thawing process kills the tumour cells as ice crystals pierce the tumour membranes destroying the cells. Cryotherapy is delivered 2 or 3 times with a month between treatments [18]. Cryotherapy may cause the eye and eyelid to swell for a few days and can damage the retina leading to blind spots and temporary retinal detachment.

Brachytherapy: Brachytherapy, also known as plaque radiotherapy, is used for small to medium sized tumours less than 15 mm in diameter and 10 mm in thickness that are situated away from the optic nerve and centre of vision. Brachytherapy can also be used as secondary measures after prior failed treatment such as cryotherapy or in the case of recurrence [6,9].

Brachytherapy involves the application of radioactive material to the outer surface of the eye (sclera) at the base of the tumour. Commonly used radioactive material includes Ruthenium 106 and Iodine 125 [33]. The radioactive material is put into a small carrier known as a plaque, which delivers a low dose of radiation directly to the tumour.

The plaque is surgically attached to the outer part of the eyeball, directly over the tumour. The plaque is left in place for between two and five days before being surgically removed. Brachytherapy has a 90 per cent tumour control rate but can lead to the development of a cataract. However, this can be corrected with surgery once the Rb is under control [33].

Local therapy: Local therapy or external beam radiation therapy was the preferred form of Rb management in the 1990's. However, the

long-term complications such as damage to nearby body tissue, the increased risk of developing secondary cancers, particularly in those patients with hereditary Rb, stunting of the orbital growth, dry eye, and cataract, led to the development of newer chemotherapy protocols [33].

External beam radiation therapy is most often used in advanced cases of Rb such as advanced bilateral cases or recurrence [3]. It is also indicated in eyes that contain one or more tumours that involve the optic disc, a tumour that is larger than 16 mm in diameter, where there is sub-retinal seeding, and for eyes where primary chemotherapy and local therapy has failed. It may also be used to treat the eye socket after enucleation if there is extension behind the area [25].

External beam radiation therapy uses an invisible form of high energy (like x-rays) to kill cancer cells or keep them from growing or dividing [28]. A linear accelerator machine directs radiation to the precise area of the eye needing treatment. However, if the cancer is extensive, radiation treatment of the entire eye may be necessary. The treatment is given in doses measured in unites called centigrays (cGy).

Ray and Gombos [3] reported a dosage of 45-50Gy given in 1.5 - 2 Gy per fraction. Radiation is usually given 5 days a week for several weeks with the delivery only taking a few minutes.

Enucleation: As a result of earlier tumour detection as well as improved use of more conservative eye-sparing treatments such as focal therapy, there has been a significant decrease in the use of enucleation in patients with Rb over the last 40 years [3]. However, enucleation remains a frequent treatment for Rb and is indicated for all unilateral tumours that fill over half the eye, where there is extensive seeding, retinal detachment, high risk of metastasis and tumour invasion into the optic nerve [3].

In patients with bilateral Rb, the eye with the more advanced tumour will be enucleated and the less affected eye managed by other therapies [7]. If neither eye has useful vision because of damage already caused by the cancer, enucleation of both eyes will be undertaken to make sure that all the cancer is gone. Thus, enucleation primarily occurs in groups D-E of the International Classification for Intraocular Rb and group V of the Reese-Ellsworth Classification of Intraocular Rb.

Enucleation is the surgical removal of the eyeball, leaving the 6 extra-ocular muscles and the contents of the eye socket intact [25]. Enucleation is performed under general anaesthesia with the procedure taking 60-90 minutes. Immediately after the eyeball has been removed, an orbital implant is inserted into the socket. The eye muscles are attached to the implant to improve motility and the implant is covered externally with the conjunctiva (pink surface tissue that lines the eyelid) and sutured in place [25].

The patient is then fitted with a conformer shell made of clear acrylic resin offering a smooth curved surface over which the eyelids blink without rubbing the suture line. The shell maintains the shape of the eye socket and helps stop infection. It has a small hole to allow drainage and is marked with a letter to indicate its size. A pressure pad is worn over the empty socket for 12 to 48 hours after the operation to help reduce tissue swelling in the socket. Side effects of enucleation include bruising, ptosis (droopy eyelid), haemorrhage, infection, scarring of the socket and extrusion of the implant [23].

Chemotherapy: Systemic therapy or chemotherapy is an effective treatment for large tumours or tumours that are located near the optic nerve or centre of vision [25]. Chemotherapy is the use of anti-cancer drugs to destroy cancer cells by stopping them from growing or multiplying [25]. The chemotherapy drugs most commonly used for treating Rb are etoposide, carboplatin and vincristine [5]. Often two or more drugs are given at the same time depending on the extent of the tumour [25].

Chemotherapy can be given in several different ways, but is most often given intravenously (IV) through a vein or orally. This is known as systemic chemotherapy [25]. Systemic chemotherapy is where the drugs travel through the bloodstream to eradicate the cancer rather than being applied directly to the cancer [18]. When given intravenously, the chemotherapy drugs travel through a device called a port-o-cath. The port-o-cath is surgically inserted under the skin of the patient's chest and is attached to large blood vessels.

The chemotherapy drugs travel through the bloodstream to enter the blood supply of the tumour where they begin to destroy it. By being directly inserted into the bloodstream reduces the risk of harm to the surrounding tissues. Systemic chemotherapy is given in cycles of treatment followed by a rest period. Each cycle lasts a few weeks with the total length often being several months; though this is dependent on how well the tumour responds [18].

These methods can expose the entire body to significant doses of chemotherapy, thus can result in unwanted and sometimes long-lasting side effects such as hair loss, mouth sores, damage to the heart, kidneys and lungs, nausea and vomiting, fatigue and increased chance of infections [34]. Intra-arterial chemotherapy is a new treatment for advanced Rb [11]. The chemotherapy drug (melphalan and/or topotecan) is delivered through the blood vessels [30].

A thin catheter is inserted into a large artery on the inner thigh and threaded through blood vessel into the ophthalmic artery. The chemotherapy drug is then infused into the artery. This method is designed to minimise the drug's exposure to the rest of the body and to reduce side effects often seen in systemic chemotherapy [18]. The average number of treatment sessions is three for each eye with each session being delivered at four-week intervals. Due to its recent development, the long-term effects of this treatment is yet unknown. However, early reports indicate up to 100 per cent globe salvage for group C and D of the International Classification of Intraocular Rb [29]. Typically chemotherapy is used in addition to other therapies in order to either shrink a tumour before other therapies, known as neo-adjuvant therapy or chemo-reduction, to destroy cancer cells that remain after therapy, for example post-enucleation called adjuvant chemotherapy or to help destroy cancer if it spreads or recurs [25].

Chemo-reduction: Chemo-reduction has become an important therapeutic tool in treating Rb [30]. Chemo-reduction is a method of using intravenous chemotherapy to reduce the size of the tumours so that residual tumours can be eradicated with focal treatment methods. This approach results in 85 per cent globe salvage of eyes classified as Reese-Ellsworth groups I to IV, compared to 47 per cent in group V [31]. Chemo-reduction coupled with focal therapies can minimise the need for enucleation or external beam radiation therapy.

Chemo-reduction is used in nearly all children with bilateral Rb and about 25 per cent of children with unilateral Rb [30]. It is most successful for tumours without sub-retinal fluid or vitreous seeding.

Extra-ocular Rib: Few patients in developed countries present with extra-ocular Rb. Extra-ocular disease may be localised to the soft tissues surrounding the eye or to the optic nerve, brain, or central nervous system.

The standard treatment options for when the cancer has spread within the eye, known as orbital and loco-regional metastasis, is chemotherapy and radiation therapy; with the cure rate standing at 60 to 85 per cent [30]. Orbital Rb occurs as a result of progression of the tumour through the sclera and occurs in 60 to 70 per cent of patients with extra-ocular disease.

Patients with stage I to III extra-ocular Rb have had an eye removed yet there is some microscopic spread to the optic nerve, lymph nodes or bone cavity. Patients with spread to these areas require adjuvant chemotherapy and possibly radiation therapy after enucleation [30]. Adjuvant chemotherapy destroys microscopic cells in order to prevent a possible cancer recurrence.

Stage IV encompasses extra-ocular spread to distant areas of the body outside of the eye such as the central nervous system. This stage of extra-ocular Rb is treated with high dose chemotherapy and/or radiation therapy to destroy as many cancer cells as possible, before being given a stem cell transplant. A stem cell transplant is where hematopoietic stem cells are given to a patient to replace bone marrow that contains cancer. These cells grow into healthy blood cells to replace the ones the patient lost [32].

Recurrent Rb: Recurrent Rb is cancer that has returned after it has been treated. The cancer may recur in the eye, (intraocular), in tissues around the eye, or in other places in the body (extra-ocular). Furthermore, the cancer may come back in the same place (called a local recurrence), nearby (regional recurrence), or in another place (distant recurrence).

When this occurs, tests will be undertaken to determine location, size and how aggressive the new tumour is. Treatment for recurrent intraocular Rb may include enucleation, external beam radiation therapy, systemic chemotherapy and/or focal therapy [28]. Treatment failure necessitates additional external beam radiation in 10 per cent of patients and enucleation in 15 per cent of patients at five-year follow-up. Recurrent extra-ocular Rb can be treated with systemic chemotherapy, radiation therapy and stem cell transplant. Long term monitoring will detect possible recurrence at an early stage, thus be controlled with further salvage measures [35].

Trilateral Rb: The optimal therapy for patients with trilateral Rb is not known, however treatment have progressively resulted in increased survival of patients in the last 20 years [35]. Before 1995 the five-year survival rate of trilateral Rb was 6 per cent compared to 44 per cent. Current research suggests that successful treatment of trilateral Rb includes screening at diagnosis and treating with high-dose chemotherapy with stem cell transplant [35].

Psycho-Oncology

Increasingly, early diagnosis is possible because of early detection [36]. As such, the focus of care has now expanded to survivorship, and in particularly, the field of psycho-oncology [37-40]. Psycho-oncology is the psychological, social and behavioural factors, and the response of patients and their families, at all stages of the disease [41,42]. It is aimed at improving the quality of survival of the patient and their family [43] and is often split into two subfields, paediatric and adult psycho-oncology. Psycho-oncology is a multi-disciplinary approach involving medical staff, psychiatrists, psychologists, neuropsychologists, social workers, schools and counsellors [44].

Although there are reports of a small percentage of cancer survivors experiencing psychological distress, it remains under-diagnosed and often undertreated in the oncology setting [45]. Unfamiliarity of the symptoms, misinterpretation, patients not subscribing to the preconception of their experience, and shortcomings of the measuring instruments used are common reasons [46,47].

Childhood cancer survivorship

When a person faces the diagnosis of cancer, they are not only subjected to changes in their physical health but also changes to self-perception and social relationships [45]. Although the majority of childhood cancer survivors adjust well to life after cancer, a subgroup of survivors experience problems as a consequence of the disease or due to the treatment [48]. This can result in adverse life-long psychological distress [43].

Distress is common in cancer patients and can manifest in the clinical syndrome of anxiety and depression or as worries, fears and stress [40-42]. This may be due to a loss of independence, reduced energy levels, lack of enjoyment in previously enjoyed activities, communication and emotional difficulties, discrepancies between anticipated and achieved goals, and maintenance of unhelpful coping mechanisms [37].

Psychosocial, clinical or maladaptive coping strategies can arise at varying times often related to developmental changes. Along with the normal developmental changes such as development of own identity, decision making and intimate relationships, childhood cancer survivors are also at risk of chronic health problems which affect academic achievement, impair or decrease social relationships and lead to low self-esteem [39]. As the childhood cancer survivor reaches adolescence, they may start to experience cancer-related concerns including the experience and consequence of physical, psychological and social changes. Often these concerns are expressed indirectly to their care team and more often when family members are not present. As young cancer survivors become settled into adulthood, educational concerns around their personal cancer history and late effects may become more important [38].

A childhood cancer survivor moving through adolescence to a young adult can experience vulnerability. Follow-up consultations based upon psycho-oncology models, and programs that are sensitive to the developmental trajectory from childhood to adulthood are of upmost importance.

The cancer survivor's family

Childhood cancer not only affects the child but also their family. Paediatric psycho-oncology care includes late effects for the child's family [43]. The majority of parents of children with cancer will act as their caregiver placing them at an increased risk of developing anxiety and depression due to changes in family dynamics, socioeconomic status and their own coping strategies [46].

Parents are most likely to worry on a daily basis about recurrence of the disease, the child's school performance, lack of friends, physical side-effects and job opportunities. This often results in the parent experiencing uncertainty, loss and loneliness [49] and with siblings experiencing loneliness and a change in family dynamics. Effective communication with their parents and attending support groups has been found to reduce some of these feelings [50].

The impact of childhood cancer on cancer survivors, their parents and siblings does not seem to decrease over time. The change in parents' and siblings' perspective of life can influence the child's mood

and coping [51]. Thus, if the child picks up on the negative emotional wellbeing of their parents and siblings, then they are likely to experience psychological distress that can impede their own emotional and physical wellbeing. These findings support the notion that psychosocial care needs to incorporate the families' strengths and limitations in order to provide the best level of support for those who need it [41].

Measures and interventions

Whilst the Quality of Life and the Health-Related Quality of Life measurements take into consideration the social, cognitive, emotional and physical functioning of the patient, assessing only the negative aspects of health, fails to distinguish between related concepts such as wellbeing and health status and variations in the sources of information, e.g. doctors overestimating physical symptoms; parents focusing on long-term effects; and the child focusing on immediate effects [51].

Without a fully functional assessment measure, the practical application of clinical interventions that addresses specific concerns of patients falls short, mostly due to a lack of information and guidance [41]. Patient's whose psychological needs are not met are less likely to tolerate treatment and late effects such as secondary cancers [52].

The Psycho-Oncology Consultation Model developed by Deshields and Nanna [41] includes goals of care and specific interventions that clinicians can use. The model advocates care of the "whole" patient which includes addressing the mental health needs of the cancer patient, facilitation of effective communication between patient and care providers, developing healthy coping strategies, enhancing self-efficacy, addressing information needs, and reducing distress.

Due to the intensity of treatment and time availability and resources, interventions should be delivered on a least intrusive and most effective basis often starting at the first session [41]. Eliciting the patient's story, their current resources for coping and support mechanisms through normalising and validation are essential to provide the patient and their families with practical, educational and social support by making efficient and effective referrals. Specific treatment options for patients experiencing clinical symptoms such as depression and anxiety include Cognitive Behaviour Therapy and relaxation, both of which have a positive long-term effect on quality of life [53].

The parents

Due to the early age of Rb diagnosis, parents become the primary decisions makers and therefore, seek an active advocacy role in their child's health care needs [54]. Confronted with information that is difficult to digest and poorly communicated, such as treatment options, risks and outcomes, parents can become easily overwhelmed and misunderstand what is being asked of them. This can sometimes result in delayed treatment decisions that may put the child at a disadvantage [54]. General and disease-specific information that is presented at a level each parent is able to understand, improves parental adjustment, increases their understanding of risk, and potentially improves outcomes and compliance with treatment [55].

Ek and colleagues [56] found that parents' emotional reactions are particularly strong after the diagnosis and first treatment of their child for Rb, with feelings of shock and unreality. This is soon replaced with feelings of emptiness, tiredness and gratefulness that their child is alive. Having somebody to confide in can ease the emotional burden experienced.

Various quality of life measures have been conducted investigating parents' own perceived quality of life and those of their children. On reporting their own quality of life, parents scored lower than the general population indicating that having a child who is cured from Rb still impacts their own emotional wellbeing [57]. This could be due to psychosocial and medical worries and fears such as their child developing secondary cancers, their education attainment and social relationships. Investigating the coping experience of parents of a child with Rb Hamama-Raz et al. [58] found that parents' strengths as individuals and partners, and their ability to separate thoughts and emotions, made them more equipped to cope leading to improved quality of life.

When asked to rate their child's quality of life, parents' perceived their general and emotional health as poor and reported more emotional and behavioural problems, despite the quality of life of their child, being no different from the general population [57]. Although parents report more behavioural problems in their child than the actual child, van Dijk et al. [59] found that both parents and survivors reported the survivor internalising their emotional and behavioural problems by becoming depressed, anxious and withdrawn. Parents may overrate the behavioural problems of the child as a result of their own coping strategies in dealing with the uncertainties and their own adjustment to their circumstances [59].

Parents of children who had bilateral Rb and those who received chemotherapy reported their child had low participation levels in community related activities, possibly due to the relationship between participation and quality of life. Sheppard et al [60] found that mothers reported their child had a good quality of life when being interviewed. However, when the same questions were asked using standardised measures, mothers rated their child's quality of life as poor. This raises questions about methodology in assessing quality of life and is worthy of further investigation.

The survivor

There is little follow up data on Rb survivors which has tended to focus on coping strategies and quality of life [60]. The use of task and avoidant orientated rather than emotion orientated mechanisms in stressful situations may account for this [61]. Enhancing certain qualities that make them better at coping with adversity puts the survivors at the same level of functioning as the general population [61]. The discrepancy between the survivor's quality of life and that as perceived by their parents appears to be a reflection of the parents' coping mechanism rather than the child's actual functioning.

Rb survivors who use emotion orientated coping strategies are likely to experience behavioural problems such as self-blame, anger and isolation resulting in maladjustment. Behavioural problems are also associated with level of social support, life events and acceptance of the disease [61]. Monitoring and support of these individuals is therefore required. With minimal literature on how to support survivors of Rb, the guidelines from the Institute of Medicine and the Psycho-Oncology Consultation Model are advised.

Ross et al. [62] found that the majority of Rb survivors exhibit good health, physical development and normal mental and motor ability. However, 39 per cent of Rb survivors needed an intervention to improve their visuo-motor development and children diagnosed with bilateral Rb needed more support than those with unilateral Rb.

Treatment intensity may be the cause of this but so may be self-care, relationships and mobility [63].

Health-related quality of life of survivors has been found to be the same as with the general population. However, they perceive their quality of life at school as lower compared to their healthy peers [57]. Willard et al [64] examined the developmental functioning of infants and young people with Rb through the first five years of their life. Their findings point to a low level range of functioning that led to a significant decline over time. This is in contrast to previous findings of survivors demonstrating above average intellectual functioning compared with the general population [65] and so is controversial.

Continual assessment of cognitive functioning in Rb survivors as they age is required to capture a full picture of intellectual functioning. Educational environment, time away from school, relationship and support from peers and teachers are crucial factors [66], as indeed is stress [67], and biomarkers of stress [68-71]. Parents, caregivers and healthcare workers often underestimate young children's understanding about their illness and their resilience. Assumptions are too often made on what a good quality of life is for the survivor and their families. Giving a voice to the survivors and their families on their own wellbeing is essential in order to create a fully patient-centred and individualised model of care that addresses lifestyle, psychological and social aspects of cancer, especially in young individuals who are just beginning to express themselves in growing up.

Summary

Chemo-reduction with or without focal therapy is the most commonly employed conservative treatment for Rb [11]. Although an effective treatment, tumour and associated vitreous and sub-retinal seeds can recur within the first 3 years [35].

Thus, chemo-reduction is most successful for tumours without sub-retinal and vitreous seeding: group A-B on the International Classification for Intraocular Rb and groups I-IV on the Reese-Ellsworth Classification for Intraocular Rb. Enucleation stands alone as the treatment of choice for patients with tumours that fill more than 75 per cent of the eye.

High-dose chemotherapy with stem cell transplant is the treatment of choice following enucleation for patients with extra-ocular Rb stage I to IV and for trilateral Rb.

The relatively small numbers of Rb cases coupled with non-comparable staging systems, for example the Reese-Ellsworth had resulted in little research into this prolific disease [31]. However, over the last twelve years collaboration between national and international centres has resulted in an increase in the evidence base of Rb management.

Current research is directed towards genotype-phenotype relationship, local drug delivery methods, minimising side effects of treatments, developing better animal models and exploring biological treatment such as growth factors [72]. Supportive treatment for the patient and their families are currently more focused upon the physical health rather than the psychological impact of the disorder.

Psych-oncology models are helpful in addressing the coping mechanisms, providing support, and providing a voice for young survivors of Rb.

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