Retinoblastoma: A Journey of 60 Years

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Retinoblastoma is a malignant tumour of the retina that is diagnosed in approximately 8000 children worldwide each year and although it is the most common primary eye cancer to affect children, it is considered rare in high resource countries with low birth rates [1–3].

19.1 Reducing Paediatric Mortality

In the 1950s retinoblastoma was associated with high mortality throughout the world. It is a paediatric cancer and so has a higher incidence in countries with high birth rates. As high resource countries have less children, the burden of retinoblastoma now falls upon low and middle resource countries e.g. in Nigeria it is the most common paediatric cancer in under 5 s [4]. Whilst there have been many medical advances in high resource countries noted over the last 6 decades, the high survival rate of greater than 95% stems from increased awareness of signs by the parents and guardians and the development of specialized centres for the treatment of the condition. It is no surprise that in countries without universal screening strategies, mortality rates have been documented of up to 60% [5, 6].

19.1.1 Lag Time

Delay in diagnosis is a pejorative term to describe the time interval between the onset of symptoms/signs and presentation to a service that can diagnose and treat the condition in a timely manner [7]. It has been demonstrated that increased lag time is associated with increased mortality for retinoblastoma [8]. This is the case in low/medium resource countries. However, in the UK it has been shown that increased lag time is no longer associated with a poorer outcomes [9] compared to three decades beforehand [10]. This is a similar finding to the US [11]. It is becoming more apparent that individual tumour biology is relevant in countries where the median lag time is around 1 month [9] and mortality is rare [11].

There have been concerted efforts to universally screen for retinoblastoma often at the same time as congenital cataracts. This is effective in

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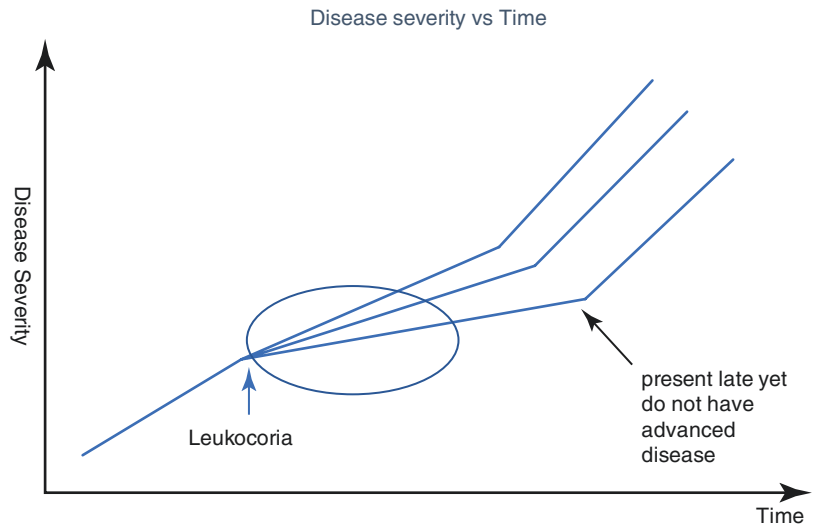

Fig. 19.1 This hypothetical chart shows that disease severity is independent of lag time in countries where the lag time is short (circled)

reducing mortality but not avoiding enucleation as early RB (Groups A, B and C) can only be detected by ophthalmologists with children under anaesthesia and this is not cost effective for the general population [12]. Kaliki et al. [13] found that only 21% of Indian patients with high-risk Rb (adverse histopathology) presented after 6 months of signs being noted which is surprising, as one would expect the vast majority to be presenting at such a late time. This suggests other factors are at play for the majority who are presenting relatively early to the service. For countries with established primary care systems, a linear relationship does not exist between lag time and retinoblastoma and individual tumour biology has become more relevant to invasiveness (Fig. 19.1).

19.1.2 Communication

In addition to presenting in a timely manner, the parents and guardians need to accept the advice given for treatment. As enucleation remains the mainstay of treatment in groups C, D and E in low/middle resource countries, refusal for enucleation is a cause of increased mortality. However, in specialised centres there is an opportunity for the families to speak to non-health care professional patient support groups (e.g.: The Childhood Eye Cancer Trust in the UK). These support workers often have relatives affected with retinoblastoma and can be instrumental in persuading families that enucleation can save a child's life with good cosmesis.

Conversely, poor communication between health care professionals will increase the risk of poor outcomes. In avoiding enucleation or systemic chemotherapy, units may use innovative treatments and this may increase the risk of metastases and therefore mortality [14]. Such decisions need to be discussed within a multidisciplinary environment including an open discussion with the families.

19.1.3 Orbital Disease

Until recently, orbital retinoblastoma was considered fatal with very little that could be done to prolong the child's life. However, a concerted multidisciplinary approach involving systemic chemotherapy, external beam radiation and enucleation can improve survival to 90% (18 of 20 cases) [15]. These are cases without intracranial involvement on MRI scanning nor metastases at presentation, but can still provide hope to clinicians and patients in countries that often see patients presenting in this manner.

19.1.4 Pinealoblastoma

In high resource countries death from retinoblastoma is rare, but mortality may be seen with children who have pinealoblastoma in addition to retinoblastoma. The survival for children who develop pinealoblastoma due to being *RB1* carriers is poor compared to those with sporadic pinealoblastoma [16].

19.2 Shift from Radiation

The first attempt to treat retinoblastoma with X-ray occurred in 1903 and was carried out by H.l. Hilgartner in Austin, Texas [17]. In 1919, Schoenberg described the use of radiation therapy in a 2-year-old girl with bilateral retinoblastoma. The eye with the larger tumour was enucleated and the less involved eye was treated by radium therapy. The tumour in the latter eye regressed and 3 years after first commencing treatment, the child was healthy with good vision [18]. Enucleation of the worse eye and radiation of the least affected eye represented standard treatment of retinoblastoma for the next 70 years. If diagnosed early enough, both eyes could be cured by X-ray irradiation [18]. Foster Moore in 1929 in London and Martin & Reese in 1936 [17] in New York confirmed that ionizing radiation could treat this type of tumour and also identified patterns of regression. Although success with externally applied radiation became apparent, ophthalmic complications were frequent. They began working with radiologists to progressively reduce the dose from 20,000 rads (cGy) to present day 3500–4500 cGy levels in order to attempt to preserve useful vision [19].

Kupfer in 1953 was the first ophthalmologist to combine chemotherapy, using a nitrogen mustard agent intravenously, with radiation therapy [20]. He believed that this would result in a reduction in the overall dose of radiation required to treat intraocular retinoblastoma. This technique was later abandoned due to the recorded immediate side effects of this chemotherapeutic agent; in some cases children died.

Forrest first wrote about the observations of second cancers in patients previously treated with irradiation for retinoblastoma in 1961 [21]. More evidence emerged confirming these finding in the years and decades that followed. Abramson wrote of similar findings in 1976 [22] and later wrote of the incidences of sarcomas and other cancers in these patients in 1997 [23].

19.2.1 Recognition of Oncology Risks to Adult Survivors

Much attention for retinoblastoma care was dedicated to saving the lives of children. However, there is increasing awareness of the risk to survivors of retinoblastoma.

It became widely recognized that patients with constitutional mutation of the *RB1* gene are at increased life-long risk of developing other specific second cancers. This risk is increased with exposure to radiation (a 50% risk of developing cancer by the age of 50 years of age if they received EBRT compared to 27% risk if they did not). These include osteosarcoma, leiomyosarcoma, malignant melanoma, lung cancer and bladder cancer [24]. Lifestyle counselling can educate survivors on ways to reduce their risk of developing a second cancer by avoiding unnecessary radiation (such as UV light) and carcinogens (such as smoking and alcohol) and obesity. They should also promptly report any suspicious unexplained lesions [25] and there have been awareness campaigns to make doctors aware of the risk to retinoblastoma survivors (Case Study).

Case Study

Caroline Aherne was a famous comedian in the UK. She had familial retinoblastoma and after treatment for retinoblastoma including External Beam Radiotherapy at St Bartholomew's Hospital in London, she was left partially sighted in one eye. Unfortunately, she suffered from bladder cancer as an adult, and later in 2014 she embarked on a programme of treatment for lung cancer. She died aged 52.

The risk of second primary cancers within the radiation field in children with germline *RB1* mutation is significant when the infant is irradiated under the age of 1 year [26]. Therefore, radiation is no longer a primary therapy for retinoblastoma.

19.3 A More Relevant Classification System

In the late 1950s Ellsworth and Reese developed a classification system for retinoblastoma. This was devised to predict prognosis and outcomes when intraocular retinoblastoma was treated with external beam radiotherapy (EBRT). It did allow international investigators and clinicians to compare results to treatment of tumour based on size for the first time.

With the advent of new therapies and the shift from radiotherapy to intravenous chemotherapy as a primary treatment for retinoblastoma, several classification systems [27, 28] developed to reflect prognosis with chemotherapy [29]. Unfortunately, they use the same nomenclature (Groups A–E) with variations of diagnostic features and therefore make comparison of publications and consensus regarding treatment difficult [30].

The TNM cancer classification system is another system used for retinoblastoma staging and was published in 2010 [31]. A revised system was published in 2016 and incorporates heritability into the classification [32]. According to this classification Group D retinoblastoma is cT2a (>5 mm subretinal fluid from the base of the tumour) and cT2b (tumours with any vitreous or subretinal seeding). It remains to be seen if this system will be used consistently by units in the future.

19.4 Increased Understanding of Genetics

The empiric risk for relatives of retinoblastoma was all that was known in the 1970s and 1980s. Offspring of patients with a family history of retinoblastoma or bilateral tumours have a 50% risk of inheriting the mutant allele and a 45% risk of developing retinoblastoma, due to incomplete penetrance. It was first reported by Knudson and later shown conclusively that 15% of patients with unilateral retinoblastoma have a germline mutation [33].

However the most accurate way to predict who will develop retinoblastoma in a family is to test them for the precise *RB1* mutant allele found in the proband. In many countries genetic testing began on retinoblastoma patients in the mid-1990s. This was gradually expanded and genetic testing offered to retinoblastoma patients in high-income and middle-income countries from the late 1990s and the turn of the century. This has been a huge advancement for patients and families.

Genetic testing of infants born at risk of retinoblastoma can be performed on DNA from amniotic fluid or from cord blood samples taken at birth. These at risk infants are examined regularly to detect early tumours. Examination without anaesthesia may be performed initially (as tumours often are within the posterior pole and mid-equatorial region) but after 2–3 months of age anesthesia is required to detect small tumours with visualization of the ora serrata essential. All children at risk should undergo multiple examinations under anaesthesia in the first 3 years life in accordance with agreed protocols. Each unit should stratify risks according to the sensitivity of screening for the *RB1* gene and previous audits of tumour detection [34]. Tables 19.1 and 19.2 demonstrate the screening strategy for offspring

Table 19.1 Screening protocol for at risk children with affected parents

	Low risk screening (risk < 1%)	High risk screening (risk 1–100%)
Starting age	Within 4 weeks	Within 2 weeks
Screening frequency		
Up to 6 months	EUA at 3 and 6 months Awake at 4.5 months	4 weekly
6–12 months	EUA at 9 and 12 months	4–6 weekly
1–2 years	At 16 and 22 months	2 monthly until 18 months 3 monthly until 2 years
2–3 years	6 monthly	4 monthly
Stop screening age	3 years	3 years at retinoblastoma unit 3–5 years: screening to be performed every 6 months by local ophthalmologist Children who have a mutation should be seen annually at a retinoblastoma unit until 16 years of age

Table 19.2 Screening protocol for children with affected sibling

	Low risk screening (risk < 1%)	High risk screening (risk 1–100%)
Starting age	Within 4 weeks	Within 2 weeks
Screening frequency		
Up to 6 months	At 3 and 6 months	4 weekly
6 months to 1 year	4 monthly	4–6 weekly
1–2 years	6 monthly	2 monthly until 18 months 3 monthly until 2 years
2–3 years	6 monthly	4 monthly
Stop screening age	3 years	3 years at retinoblastoma unit 3–5 years: Screening to be performed every 6 months by local ophthalmologist Children who have a mutation should be seen annually at a retinoblastoma unit until 16 years of age

and siblings in the UK. Recently, it has been shown that survivors of retinoblastoma (particularly women) have fewer children if the risk is unknown or they do not understand the implications of the genetic testing. This emphasizes the importance of providing information to families in a manner that they can understand [35].

19.5 The Role of Enucleation

All eyes with features suggestive of imminent extraocular extension (IIRC Group E) still require immediate enucleation. The reason for this is that there is an increased chance of high-risk retinoblastoma on histopathology with secondary glaucoma and iris neovascularization, which are deemed Group E retinoblastoma in all classification systems [13]. Kaliki et al. compared 145 cases with high risk features and compared with 258 cases without high risk features. As expected secondary glaucoma increased the risk, but only 63% developed high risk features so that 37% did not have high risk features and therefore had no increase in the risk of metastases. Similarly only 53% with iris neovascularization had concomitant high-risk features on histopathology so almost half did not. As retinoblastoma surgeons are unsure as to which eyes harbor the adverse histopathology at present, it is safer to enucleate these eyes.

Historically, many children were not fitted with an orbital implant following enucleation, as it was felt that it would interfere with the detection of tumour recurrence by not allowing for palpation of the orbit [36]. However the emergence of MRI allowed for the imaging of the orbit despite the presence of an implant. In addition, a good cosmetic outcome is achieved by replacement of the volume of the eye with an implant deep in the orbit and has also been proven to be beneficial for orbital growth [37].

Changes in the techniques of enucleation and the types of implants used have changed over the last few decades. Expensive porous implants that become vascularized with the muscles sutured to the implant had been used extensively in the past. However, they were noted to be susceptible to infection and extrusion over the years. Equal artificial

eye motility has been shown with the use of the cheaper polymethyl methacrylate (PMMA) implants and muscles sutured to the conjunctival fornices (myoconjunctival technique) rather than on front of the implant [38, 39]. The role of the prosthetist is very important in achieving the motility in the studies and it has been difficult to achieve the results in children of other ethnicities who do not have the well-formed posterior tenon's that Indian children possess. Additionally, the use of a prosthetic eye conformer at the time of the enucleation results in a positive psychological benefit to the parents and child and these conformers have been adopted internationally more recently. This is particularly relevant in countries with high mortality such that compliance with this treatment becomes acceptable.

As discussed below, some units may enucleate more children for valid reasons taking into account risk factors for metastasis. The role of child play specialists cannot be understated for these children and, if possible, it is important that long term follow-up is provided so that psychosocial concerns are addressed in a timely manner. An excellent way of providing this includes children teaching younger children about prosthesis management (http://www.bbc.co.uk/programmes/p05d4m8d).

19.6 Systemic Chemotherapy

The use of the nitrogen mustard group of chemotherapeutic agents, particularly triethylenemelamine was largely abandoned in the late 1960s [19]. However, systemic chemotherapy became important again for primary treatment of intraocular disease in the 1970s when drugs that had been shown to be effective in metastatic disease (cyclophosphamide, vincristine and doxorubicin) were also noted to have a dramatic effect on reducing the size of the intraocular lesions. It was noted though that the lesions regrew after stopping the chemotherapy treatment. However, alternatives to external beam irradiation were sought in the 1990s [40].

From 1996 [41], the first-line treatment to control Murphree IIRC Groups B, C and D retinoblastoma has been intravenous chemotherapy with different combinations, doses, schedules and durations of carboplatin, etoposide and vincristine (CEV) followed by focal therapy with cryotherapy or laser, applied to consolidate chemotherapy responses [42] and to destroy any recurrent tumour [41, 43]. CEV is generally given every 3 weeks through a central venous line. Intravenous chemotherapy alone eradicates the retinoblastoma completely and regular, frequent examinations under anaesthesia are necessary to observe for relapses or recurrences following completion of chemotherapy treatment [44, 45].

19.7 Focal Therapy

Focal therapy is the local application of treatment to the eye under direct visualization i.e.: laser, cryotherapy or plaque. It has become the primary treatment for IIRC Group A eyes and is also used to consolidate responses of IIRC Group B, C and D eyes following intravenous or intra-ophthalmic arterial chemotherapy.

19.7.1 Laser

In Germany in the 1950s, Gerd Meyer-Schwickerath developed photocoagulation using a xenon arc beam [17]. It was noted that this could be used for small retinoblastoma tumours (1–4 mm in diameter) and it was called light coagulation. It was also used to treat recurrences following plaque or EBRT during this time [17].

Its use continued through the following decades and currently still plays an important role in treatment of IIRC Group A and B eyes and to those tumours that have been initially shrunk by chemotherapy. As with many treatments for retinoblastoma, the evidence for laser in patients having chemotherapy is not robust [42] yet it is standard treatment for many centres. Transpupillary thermotherapy involves directing 810 nm diode laser through the dilated pupil to heat the tumour for 3–5 min per spot. Photocoagulation therapies with 532 nm, 810 nm

or continuous-wave 1064 nm laser beams are directly applied by multiple short burns. The power is gradually increased until the tumour is coagulated and grey to white.

19.7.2 Cryotherapy

Cryotherapy was introduced by Harvey Lincoff et al. in the 1960s [18] and became an important adjunct in the treatment of peripheral or anteriorly-located small retinoblastomas [17]. It can be used for more posterior tumours where central visual damage will not result. Cryotherapy involves freezing the tumour through the sclera with a nitrous oxide probe. The tumour cells die during the thawing stage and therefore a full 1 min interval between each freeze cycle is important. A triple-freeze thaw technique is used.

In general, focal therapies are repeated 2–3 weekly until the tumour is completely atrophic.

Whilst a flat scar can be easily achieved using cryotherapy, repetitive laser sessions are necessary to create a scar after chemotherapy and laser (dependent on the size of the original tumour). As a result it has been advocated that certain phenotypes that do not flatten with post chemotherapy laser (e.g. cavitary retinoblastoma) do not require repetitive laser after chemotherapy [46].

19.7.3 Radioactive Plaque Therapy

Stallards' collaboration with Innes in 1964 led to the development of Cobalt-60 applications of varying size which could deliver a dose of 4000 rads to the apex of the tumour in 7 days at St Bartholomew's Hospital, London [19]. This was the beginning of modern-day brachytherapy and plaque therapy later began in the United States in 1969.

Episcleral radioactive plaques such as the iodine or the ruthenium plaque have become another form of focal therapy option. Plaque focal radiation is effective at treating single recurrences after chemotherapy or EBRT had failed. In some instances, where a single tumour of less than 13 mm in diameter exists, not adjacent to the optic disk or macula, it may be treated with a plaque as a primary treatment. Its use has recently declined as it is recognized that it may result in haemorrhages and retinal detachment if used prior to intra-ophthalmic arterial chemotherapy [47].

19.8 Intra-Ophthalmic Artery Catheterization (IAC)

Intra-arterial catheterization has been used for eye salvage therapy in Japan since the 1990s using a balloon to block the carotid artery and direct chemotherapy flow to the ophthalmic artery. In 2006, Abramson and colleagues modified this technique to achieve a more selective delivery to the eye via catheterization of the ophthalmic artery (intra-ophthalmic artery chemotherapy). Reported results were encouraging with high eye salvage rates [48–50]. Indications for IAC use soon expanded to include primary treatment. One study demonstrated overall globe salvage was 74% when IAC was used as first-line treatment and 67% when used as second-line treatment [50]. Additional chemotherapeutic agents were added later including topotecan and carboplatin.

The early adopters of this treatment may have given this treatment to group E eyes with a 50% risk of high risk features and as a result children may have died. Therefore, it is not universally adopted [51]. Another concern is vision (see below) when used for non-macula tumours.

19.9 Widespread Use of Intravitreal Chemotherapy

Historically, one of the most difficult features to control in the treatment of retinoblastoma was that of vitreous seeding, and it was one of the main causes of failure of primary treatment [52]. Again intravitreal chemotherapy was performed for decades in Japan before a safety enhanced method was introduced by Munier et al. in 2012 [53]. Following the use of this methodology, it has been acceptable to virtual all units.

Encouraging results have been emerging over the last 3 years [53, 54]. Vitreous seed median time regression has been reported at 0.6, 1.7 and 7.7 months for dust, spheres and cloud seeds respectively. The median number of injections required to reach regression was 3, 5 and 8 injections for the respective seed groups [55, 56]. Metastatic spread has been shown in a systematic review to be a rare occurrence [57]. Topotecan is another agent recently being used for recurrent seeds [58].

19.10 The Battle for Group D Eyes

Virtually all units will salvage Groups A, B and C eyes and enucleate Group E eyes with certain phenotypic characteristics. Controversies arise for Group D eyes with some advocating enucleation in all unilateral cases and some advising salvage at all times. Unfortunately, there is no consensus on the definition of a Group D eye (as discussed above) and this makes comparison between different centres difficult.

19.10.1 Discussion with Parents

The discussion with parents is essential. Generally, parents would like to save the eye if it is safe to do so. Uncommonly parents may be keen for enucleation, e.g. a recent relative has died from chemotherapy for a non-retinoblastoma cancer and they would like to minimize the use of chemotherapy. Parents need to be aware of the risk of enucleation after the attempt to salvage, visual potential and the treatment burden in terms of number of examinations under anaesthesia.

In London, the success rate for salvage for Group D eyes is 63% with 55 months median follow-up and no children receiving first line IAC nor suffering metastases [59]. Children who undergo enucleation have three times fewer EUAs compared to those who have salvage treatment [60]. This is important information as parents are concerned about the risk of multiple anaesthetics on their children particularly neurodevelopment [61]. Unfortunately, even if enucleation was to take place and adverse histopathology identified with appropriate adjuvant chemotherapy, there is still a risk of metastases of up to 4% [13, 62].

19.10.2 Type of Treatment: Systemic vs Intra-Ophthalmic Arterial Chemotherapy

13% of Group D eyes [27] are associated with high risk features [63]. Interestingly vitreous seeding appears to be a good sign for the avoidance of high risk features in the 10 of 62 eyes exhibiting this feature. All patients were treated with systemic chemotherapy and none developed metastases. IAC may also be used to treat Group D eyes but metastases have been noted in 3% (3/103) [64]. None of the children who had metastases died.

Our approach is to advocate first line IAC for children with group D eyes and vitreous seeding and to use systemic chemotherapy for Group D eyes without vitreous seeding.

19.11 The Role of Vision

With more eyes being saved, the retinoblastoma specialist must now also consider long-term visual acuity when choosing therapies and counselling families. It has been shown that up to 58% of eyes maintain vision of better than 6/12 (20/40)

[65, 66] when they are old enough to perform Snellen visual acuities. However, the reports relate to eyes independently and it is important to be aware that early support for visually impaired infants from any cause will provide life-long benefits [67]. As a result a delay in assessing vision in infants and sending to the appropriate visual rehabilitative service can have far reaching effects. Therefore, it is essential that vision is assessed in pre-verbal children using appropriate paediatric ophthalmological tests.

Visual potential is an important consideration in the discussion with the family regarding enucleation of an eye or attempts at salvage. With particular relevance for Group D eyes, half had better vision than 6/60 (20/200) and 7 of 32 (22%) had better than 6/12 (20/40) vision [68].

It is also relevant for new treatments. Rather than wait until young children being treated are old enough to perform tests suited for adults, it is important to identify complications early and address the causes. This means the assessment of pre-verbal children by appropriate tests and the use of visual evoked potentials. Retinoblastoma units were initially tentative in their use of IAC due to complications including choroidal ischaemia and visual loss [47]. Vision in previously seeing eyes was initially lost in 42% of patients [69] which was thought to be due to the learning curve for interventional neuro-radiologists. However, Reddy et al. [70] showed that patients with similar catheterization complications yet a reduced dose of melphalan did not lose vision.

19.11.1 Patient Centred Approach

The vast majority of patients are under 5 years of age and therefore a patient centred approach needs to consider that these are children not adults. Until recently there was little consideration of the non-medical concerns of children with retinoblastoma. However, there is now a desire to address psychological issues, particularly regarding the parents [71] and make the multiple EUAs that they have to endure as painless as possible. Families benefit from the presence of a patient support group representative (e.g. The Childhood Eye Cancer Trust in the UK) at diagnosis and subsequent visits to address non-medical concerns but also to raise questions that they feel they cannot ask the health care professionals. As a result, it is important for the psychologist and patient support group representative to be part of the multi-disciplinary meeting so that psychosocial concerns can be addressed. This integrated team approach can optimize patient care.

19.12 Conclusion

Over the last 60 years, the management of retinoblastoma has been revolutionized with the advent of novel therapeutic modalities, diagnostic imaging, improved chemotherapeutic agents and approach to children. The gradual shift from EBRT to systemic chemotherapy has improved survival and also helped with greater rates of eye salvage. The survival rate of retinoblastoma in high resource countries was 90% in 1997 and that rate is now over 95% in 2017. The adaptation of intra-ophthalmic artery chemotherapy and intravitreal chemotherapy has also improved eye salvage rates and the retention of vision.

Significant challenges remain however. Retinoblastoma in low-income countries is associated with low patient survival of approximately 30–40%. This is a statistic that needs to be improved. The creation of toolkits (Fig. 19.2) and international collaborations can and will improve survival.

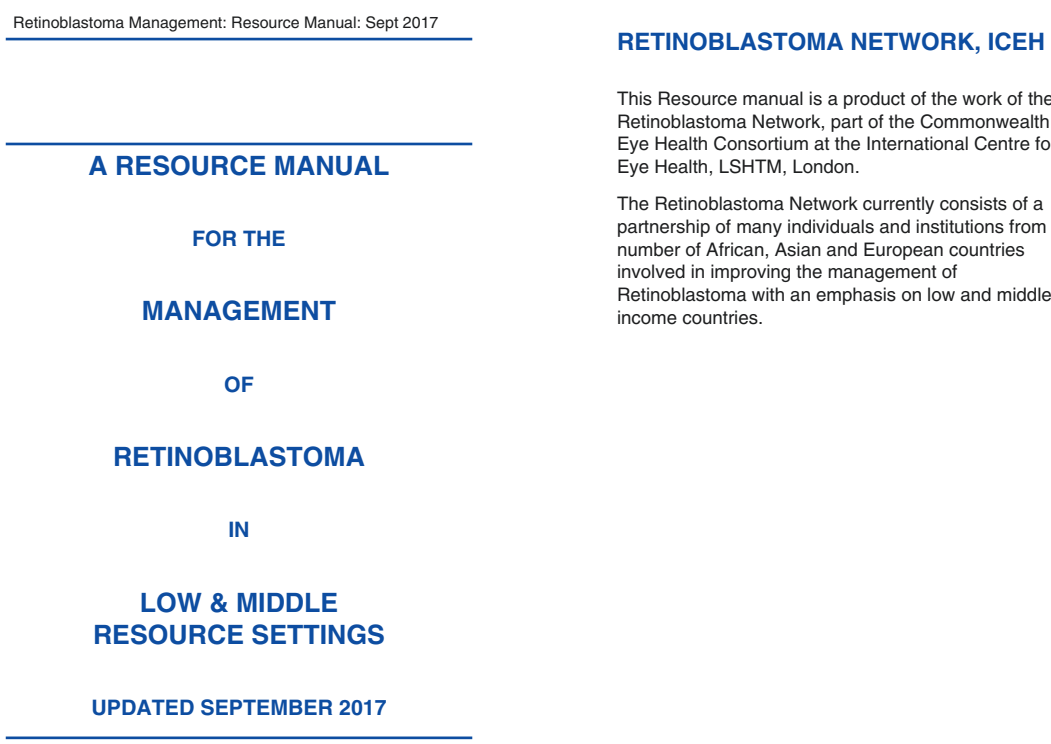

Fig. 19.2 The development of a toolkit to assist in the development of a Retinoblastoma Service

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