Chapter 11

General discussion and recommendations for the future
General discussion

Removal of the eye versus eye-sparing treatment modalities

Enucleation has always been the mainstay of treatment for retinoblastoma. It is, however, a mutilating intervention and results in uni- or bilateral blindness. Hence the quest for eye-sparing alternatives.

External beam radiation therapy was the first eyeball-sparing treatment that was effective for large tumours. Initially, good results were reported with high survival rates, preserved vision, retaining of the eyeball and thus a normal appearance. Studies with a longer period of follow-up, however, revealed negative effects: growth retardation of the orbits and mid-face, retraction of eyelids, cataract, radiation retinopathy, damaged lacrimal systems and increased chance to develop second primary malignancies. This treatment modality is now almost completely abandoned.

Currently, locally administered chemotherapy is thought to be a promising alternative to enucleation. In recent years, a shift is observed from enucleation to intra-arterial chemotherapy (IAC), also referred to as ophthalmic artery chemosurgery (OAC). With lower-grade retinoblastoma stages in particular, IAC is increasingly performed, reducing the need for systemic chemoreduction with its potential harmful effects such as ototoxicity. From a technical point of view, IAC is considered minimally invasive, but systemic adverse effects such as hemodynamic instability, femoral artery occlusion, hyperaemic cutaneous periorocular abnormalities and cerebral vasoconstriction have been reported. Ocular complications include retinal and choroidal vascular toxicities such as ophthalmic artery thrombosis, choroidal non-perfusion and retinal and vitreous hemorrhages. Moreover, IAC is not always effective and proper patient selection is required. In a recent study, the five year’s ocular survival for advanced tumours (group D and E) treated with IAC was reported to be 70.2%. In a recently published review, refractory and recurrent tumours were seen in a total of 130 IAC treated-eyes from 8 studies, resulting in secondary enucleation in 36 cases (27.7%). Furthermore, the recent development of supplemental treatment with intravitreal chemotherapy injections in eyes with vitreous seeds and refractory or recurrent tumours increase the globe salvage rate without compromising patient survival. Long-term effects of IAC and intravitreal chemotherapy are still unknown. Apart from the potential complications, another negative feature of this treatment modality is that it requires repetitive treatment cycles under general anesthesia.

Enucleation has the advantage over eye-sparing modalities that one obtains material for histopathology which can be used to assess risk factors of dissemination and to determine the heritability by studying the tumour DNA. Kaliki et al. reported metastatic risk factors in 23% (117/519) of enucleated eyes. Risk factors for metastasis may be missed, but also masked in patients treated with chemotherapy. In patients who underwent secondary enucleation, the pathologic evidence of extraocular extension can be downstaged due
to the chemotherapy and can lead to increased risk of metastatic death due to reduced surveillance and subsequent treatment.\textsuperscript{13}

According to a survey from 2014, IAC is used for the first line treatment of group D unilateral and bilateral retinoblastoma in respectively 71\% and 38.7\% of centers across the world.\textsuperscript{14} The majority of centers (74.2\%) not applying IAC as treatment modality (49.2\%) are in middle or low income countries. Especially in North America and Japan, but also in Europe, IAC is used more frequently as an alternative to enucleation.\textsuperscript{14}

The decision what treatment to apply is affected by the stage of the disease, the visual potential of the affected eye and the local availability of different therapeutic options. In many middle or low income countries a delay in diagnosis is often seen due to socioeconomic factors. In combination with the lack of access to globe-saving therapies, enucleation is often the only choice to save a retinoblastoma patients’ life. For retinoblastoma stage E enucleation followed by histologic analysis and if necessary conjunctive adjuvant chemotherapy remains the only evidence-based curative treatment.\textsuperscript{15}

However, the physicians’ decision can lead to resistance of the parents and especially in middle and low income countries initial refusal of enucleation is a major obstacle leading to treatment delay which is directly correlated with advanced stage of retinoblastoma at surgery and decreased survival rates.\textsuperscript{15} Also treatment abandonment in between cycles of chemotherapy is a severe problem reported to be as high as 41.6\% in an Indian study.\textsuperscript{16} Parental refusal of enucleation in high income countries ranges from 0-25\%.\textsuperscript{15}

One can identify a number of barriers to the acceptance of enucleation. The concept of retinoblastoma being a fatal illness is one of them. When convinced that the cancer will lead to death anyway, a mutilating intervention as enucleation becomes unacceptable. Many doctors and patients are worried about the esthetic outcome of enucleation and in some cultures, the removal of an eye can be socially unacceptable. Depending on the health-care system, the cost of surgery can be a concern, but this will also have an impact on other expensive treatment modalities. It is important that the treating physician and other care providers adhere to a proper shared decision making practice, with adequate guidance of parents on expectations and risks of alternative treatments, specific to the individual patient. And in some instances by breaking down the barriers by addressing the fears and misconceptions.\textsuperscript{17}

Soliman et al.\textsuperscript{18} compared the socioeconomic impact in children with primary enucleation compared to children receiving eye-sparing treatment. They concluded that primary enucleation was associated with significantly fewer negative financial, social and psychological impacts on families than attempted eye-sparing modalities.\textsuperscript{18} In this study eye-sparing treatment did not only include local intraocular chemotherapy, but also systemic chemotherapy with focal therapy and EBRT. Of the 32 patients receiving eye-sparing treatment, 25 (78\%) were eventually enucleated due to failure of tumour control (n = 11) or because of the psychologic, financial or social burden of the cumulative therapies (n = 14). Treatment duration was negatively correlated with socioeconomic impact.\textsuperscript{18}
Implant material and implantation techniques

In the history of enucleation, various techniques and materials have been attempted and used, leading to improvements in cosmetic results, and a decrease in the number of complications. Initially, solid implants were made of glass and after the Second World War, other materials as silicone and acryl were used. The hydroxyapatite implant was the first porous implant introduced in the early 1990s. Its porosity was supposed to facilitate fibrovascular ingrowth, increasing the integration of the implant. This was thought to reduce infection rates and to improve the motility of the implant. Also, the porous material was suitable to be drilled into after implantation. A pegging system connecting the implant with the prosthesis would further enhance artificial eye motility. Improved motility of the (non-pegged) porous implant compared to the non-porous implant could not be confirmed. With supplemental pegging an increase in prosthetic eyemotility was found. Pegs are however almost abandoned by now due to complications such as increased discharge, extrusion, pyogenic granulomas, pain and implant infection. Nevertheless, many surgeons remain convinced of the superiority of the porous implant. There is a lack of comparative studies regarding the implant use and surgery technique. To identify the most frequently used materials and methods, a digital survey (Chapter 3) questioning used materials and techniques was sent out to retinoblastoma surgeons worldwide. Remarkably, 41 different methods (implant and wrapping materials and muscle attachment techniques) were reported by 58 responders from 32 countries. Porous implants were preferred over non-porous implants (58.7% versus 32.6%) and a little over half of the surgeons (54.3%) did not use any kind of wrapping. Reasons for using a specific technique or a specific material were mainly personal experience, personal believe in equality or superiority compared to other methods and materials.

Also opinions on the positioning of the muscle attachment to the implant differed. Two independent surgeons reported positioning the rectus superior more posteriorly to prevent ptosis. This was based on personal experience. The relationship between ptosis and anterior rectus superior muscle location has not been discussed in the literature before. One paper, however, postulated that the levator complex needs adequate orbital support to sustain its delicately balanced mechanism, avoiding displacement of the pivot point (the transition point where the levator muscle becomes aponeurosis and where the muscle is suspended to Whitnall’s ligament and changes in direction). In our study, presented in chapter 6, we found a relationship between increasing implant sizes and ptosis in our pediatric treated population. In our practice, the muscle positioning is uniform, regardless of the implant size. This would imply that the superior rectus muscle is more stretched with the use of a larger implant. This could potentially disrupt the levator complex. To overcome the increased stretch on the rectus superior one could position this muscle more posteriorly.

In Chapter 2 we evaluated functional complications of different enucleation materials in our own cohort of 216 patients with 23 years of follow-up. We compared these data with...
previous studies (n = 16) reporting on functional outcome of enucleation for retinoblastoma. We found that primary implant insertion using either hydroxyapatite or acrylic with donor sclera wrapping is safe and results in low rates of complications, but that hydroxyapatite implants with scleral wrapping account for an slightly increased number of exposures than scleral wrapped acrylic implants. The low rate of functional complications (exposure and extrusion) found in our cohort might be attributed to our scleral wrapping technique. In studies of De Potter et al.\textsuperscript{24} and Christmas et al.\textsuperscript{25} equally low complication rates with donorsclera-wrapped implants were reported. Unfortunately, many countries have banned the use of donorsclera out of fear for disease transmission. Without wrapping, complication rates are remarkably higher and exposure rates of 21.6 - 61.5\%\textsuperscript{26–28} with bare implants are reported. Expensive alternatives are available such as implants with prefab wrappings or implants with a smoothened surface to reduce conjunctival rubbing. Reflecting our good results we recommend the use of inexpensive implants with donor scleral wrapping, when accessible.

Additional tumour therapy significantly increased complication risks such as exposure, extrusion and also contraction of the socket. An important finding is that the socket complications of EBRT were more severe when no implant was inserted. We therefore advice to insert an implant even though additional therapy is needed. In the Netherlands we have temporarily inserted the Allen implant. The implant had a flat anterior surface at which the 4 recti muscles were attached, and it was thought that this design would better translate the implant movements to the overlying ocular prosthesis. The position of the Allen implant, however, appeared to tilt within the socket and resulted in prosthetic fitting problems, resulting in a high incidence of implant removal. This implant type has long been abandoned, yet it taught us that the implant should have a spherical design.

Motility is often mentioned as an important factor in the choice of a specific technique or material. However, a reproducible method to measure motility in children was lacking. In chapter 5 we implemented the iView\textsuperscript{TM} Eyetracker and demonstrated an easy and highly reproducible method to compare motility of the prosthetic eye in relation to the contralateral eye. In our pediatric cohort we could not measure a prosthetic ocular excursion difference between small implants (14 and 16 mm) and large implants (20 and 22 mm). This is in contrast with the study of Custer et al.\textsuperscript{29} Furthermore, we found no difference between the vascularized and integrated hydroxyapatite or the solid acrylic implants. This is in agreement with an earlier published Dutch study by Colen et al.\textsuperscript{20} and with the study of Custer et al.\textsuperscript{29} Thus, unless there is desire to peg we don’t see additive value of porous implants. Although not properly tested, we do not expect that changing the shape of the implant (to for instance a conical shape) could improve motility since a non-spherical shape would limit rotation of the implant in the socket. We believe that the major limitation of prosthesis motility is tightness of the space in which it can move. Prosthesis motility is by a fair deal determined by the location and movement of the fornices. The myoconjunctival
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technique (in which the sutures of the rectus muscles are passed through the overlying conjunctiva for attachment to their respective fornix) is the one technique responding to this limitation. Studies by both Shome et al.\textsuperscript{30} and Yadava et al.\textsuperscript{31} demonstrate improved prosthetic motility using the myoconjunctival technique. We recommend this surgery technique to be subject of future studies.

Implant size versus cosmetic outcome

As mentioned in the previous paragraph, we could not demonstrate a difference in motility comparing small and large implants. In chapter 6, we focussed on the cosmetic results with and without implant insertion and also after treatment with EBRT. A common belief is that larger implants allow for better cosmetic results. Therefore, today’s tendency is to insert the largest implant possible to fit in the socket. However, we assessed (chapter 6) a significant negative relationship between the size of the implant and the upper eyelid position, which is of great importance for the cosmetic outcome. Within the group of unilaterally enucleated patients categorized as bad or poor cosmetic result, 62\% had a ptosis. We found that with increasing implant size, the risk of ptosis increased significantly. In our study, children without ptosis were younger at enucleation than children with ptosis. The age at enucleation was correlated with the implant size: the older the patient, the bigger the implant. In adults a ptosis is relatively easy to correct under local anesthesia, but in children an additional general anesthesia is needed, and surgery results are not always predictable as the eyelid height cannot be checked during general anesthesia. The other assumed beneficial effects of a large implant include better orbital symmetry, less volume deficiency, less lower eyelid laxity because the prosthesis will be thinner and better motility. However, none of these assumptions appeared true when we compared large implants (20 and 22 mm) with medium-sized implants (18 mm). Orbital symmetry was not significantly different comparing the enucleated orbit with the contralateral side. Also in patients treated with bilateral EBRT orbital symmetry was observed, although these orbits were smaller compared to non-irradiated orbits. This was already recognized in 1996 by Imhof et al.\textsuperscript{3} Volume deficiency was more often seen in patients without implants or with small implants (14 and 16 mm). Although we could not find a relationship between implant size and thickness of the prosthesis, we did see a relationship between the positioning of the lower eyelid and the prosthesis thickness: thick prostheses showed more lower lid sagging, thin showed reverse ptosis. In contrast to the design and size of the implant, these prosthesis properties have not been subject to studies, but seem to be of equal importance. Moreover, in addition to eyelid positioning, the shape of the prosthesis may play an important role in its motility. Taking these results into account, and considering that the ocular prosthesis fitting and design is more difficult with a larger implant (remarks from ocularists), we advise insertion of an implant size of 18 mm in children until at least the age of 3. Kaltreider et al.\textsuperscript{32} proposed the formula: axial length minus 2 mm. Since the eyeball
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of a child is at 85% of its size at 2 years, the approximate mean axial length at enucleation for retinoblastoma would be 20 mm, resulting in an 18 mm sized implant, according to the formula. This corresponds with our advice.

Socket problems and management strategies

We found that discharge and infection of the postenucleation socket is a common problem in prosthesis wearers. Discharge and infection of the postenucleation socket is difficult to quantify due to its recurrent character and difference in subjective experience. Furthermore, a small amount of discharge seems unavoidable. In our cohort we could not find a relationship between personal cleaning habits and experience of complaints. This contrasted with the report of Pine et al. who found an association between cleaning regime and frequency-, volume- and viscosity of discharge: more severe discharge was reported with a more frequent cleaning regimen.

Young patients are more prone to flares of socket discharge. Since this is frequently associated with a (secondary) bacterial infection we advise to treat these patients with topical antibiotics. In a small number of patients this treatment does not reduce symptoms. In non-responders to antibiotics with chronic complaints, a specific individual approach is needed due to variation in personal habits and specific causes. In chapter 7, a decision-tree is presented, designed to systematically evaluate the potential cause for the individual patient, leading to an individualized approach.

A hypothesized cause of discharge accumulation and increased mucus production is the hydrophobic character of the prosthesis. A new technique rendering a prosthesis hydrophilic by coating the PMMA with polyethylene glycol (PEG) is promising. The hydrophilic surface will lead to a homogeneous tearfilm which in turn might reduce irritation, discharge and infections. Currently a clinical trial with the application of hydrophilic surface of the prosthesis is carried out.

Another problem identified in our study population is postenucleation socket pain. This is a rare late effect and diagnosis of the underlying cause is difficult. If no anatomical or functional causes are identified using our decision-tree (chapter 7) and treatment with pain killers or steroid injection is not sufficient, surgical exploration of the socket can be performed with explantation of the allogenic solid implant and insertion of an autologous dermis-fat implant instead (chapter 8). This, has been reported as an effective method for pain relieve. However, it is possible that this positive effect has other causes such as removal of scar tissue or neuromas. The cause of pain is probably multifactorial. In our cohort removal of the implant for exchange of a dermis-fat implant was effective in one case as well (chapter 9). A less invasive approach is destruction of nerve fibres by alcohol injection into the socket. This ancient treatment modality seems to be forgotten, but was often used in painful blind eyes due to glaucoma. Chemical neurolysis of the nerve fibers induces a transmission depression or complete destruction.
of alcohol the reported pain-free period varies between one and two years.\textsuperscript{39–41} The risk of complications is low but there are reports of transient ptosis, chemosis, lid swelling, transient facial paresthesia, sterile orbital cellulitis, and orbital hemorrhage.\textsuperscript{39,40,42–48}

The fit of a perfect prosthesis may be challenging in children. 3D planning and printing is a promising technique to design custom made conformers to improve the shape of the socket in the healing process and to improve prosthesis fitting (chapter 10).

**Recommendations for clinical practice**

In this thesis, we evaluate the sequels of enucleation and/or external beam irradiation for retinoblastoma. Enucleation is a save and very effective procedure with low complication rates and with satisfying cosmetic results as judged by patients and their parents. Our research has shown that worldwide, for the cosmetic rehabilitation, a wide variety of implant materials is used, but that complication rates (exposure, extrusion) do not differ greatly. Thus, there seems to be no harm if each center continues to apply the materials it is experienced with and satisfied with. However, if a choice needs to be made, the acrylic implant is a little superior compared to other implants: it is the least expensive implant and shows the lowest complications rates.

An individualized treatment planning is required, considering the tumour extent, additional risks and psychological impact. Furthermore, the size of the implant should not be as large as possible, which used to be the common practice. Large implants increase the risk of ptosis, possibly due to extreme stretch on the levatorcomplex resulting from the anterior positioning of the recti muscles. In order to prevent extreme stretching and ptosis, it may be studied to position the recti muscles more posteriorly.

We advise the use of a medium sized spherical implant of 18 mm after enucleation in children younger than 3 years.

Close follow-up of the operated child is needed to prevent or identify complications at an early stage when minimally invasive solutions are still effective. Topical antibiotics are primarily recommended to treat infected sockets, which are recognized by their hyperaemic state and increased (purulent) discharge.

Adequate counselling, not just about potential complications but also about alternative treatment options will improve long term outcome and satisfaction of the patients.

**Research in progress and recommendations for the future**

The appearance of a prosthetic eye differs from that of a normal eye in two respects: the lack of motility and the lack of a dilating pupil.

The size of the pupil changes constantly and is often rather large in children and young adults. Thus, the pupil size of the prosthesis may markedly differ from the pupil size of
the healthy fellow eye. This will be especially notable in patients with low pigmented irises and may betray the fact that one wears an eye-prosthesis. With the latest developments in technology, a prosthesis with an artificial pupil that can enlarge and contract as a normal pupil is no longer an utopia. The Technical University (TU) Delft developed a prototype of a prosthetic eye with a dilating pupil using the Electrowetting principle, (see Figure 1). With this technique a black droplet (representing the pupil) changes in dimensions based on light-induced electrical changes of the underlying electrode. This model is very promising, but is not yet optimal in its function and requires further adaptations. The VU University medical center and TU Delft will continue to work on this development on a collaborative basis.

The motility of a prosthesis can be further improved using our new technique for motility measurement. As the shape of a prosthesis could potentially influence the motility of the prosthesis, we started a study of the prosthetic excursions with different shapes and sizes of the prostheses.

Figure 1. Electrowetting model using a droplet as dilating pupil.
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Furthermore, we will continue to develop the 3D designing and printing techniques of the postoperative conformers and prostheses. This will improve the personal fit with hopefully subsequent reduction of complications.

For the experienced problems of socket discharge, methods that alter the surface characteristics of an ocular prosthesis have the potential to reduce these complications.

There is belief, that immediate insertion of a temporary prosthesis (although not yet perfectly fitting) positively influences the acceptance of the loss of an eye. A multi center trial study has started to evaluate the psychological effects of insertion of a temporary prosthesis in comparison to a transparent conformer (which has been our current practice).

This thesis focussed for a great part on the cosmetic outcome of survivors treated for advanced retinoblastoma. It reveals the necessity to continue evaluation and to proceed development of mainstream techniques. Further studies on late effects and cosmetic outcome of extensively treated eyes with IAC and intravitreal chemotherapy are recommended.

Delay in presentation of retinoblastoma is important for survival and required extent of treatment. Awareness campaigns such as conducted by The Eye Cancer Foundation and national screening programs may reduce the number of patients with advanced retinoblastoma, subsequently reducing the number of enucleations.

In conclusion, eye-sparing treatment modalities that can totally replace enucleation worldwide have not been found yet. In the near future, enucleation will remain an important treatment option for retinoblastoma patients. We know that enucleation saves the lives of retinoblastoma patients in up to 98%, but little was known on how retinoblastoma patients appreciate their artificial eye, what physical complaints they have and which postoperative complications they may encounter after enucleation.

Although most studies focus on treatment efficacy and patient survival, cosmetic outcome of the treatment is a very important aspect for the patients’ quality of life (QoL). Having been bullied in childhood about the appearance of their eye, ocular prosthesis or face (which can be altered due to EBRT) is negatively correlated with the retinoblastoma patients’ QoL.49 Removal of an eye has a negative stigma.

This thesis shows that patients and parents are quite satisfied with the cosmetic outcome and that enucleation is not as mutilating as previously thought. Furthermore, there is room for improvement of current materials and techniques. We hope that this knowledge will influence future decision making, where enucleation should receive the attention it deserves as a valuable treatment alternative for a devastating disease as retinoblastoma.
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References

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