Chapter 12

Summary
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In this thesis we evaluated the clinical outcome of retinoblastoma (Rb) survivors treated with enucleation and/or external beam radiation therapy (EBRT). We focused on 5 main aspects: 1. Functional complications 2. Satisfaction of the patient. 3. Problems encountered with the artificial eye 4. Cosmesis: which cosmetic alterations and potential insufficiencies are seen (regarding volume, symmetry, eyelid positioning, artificial eye motility)? Which factors are of influence, what can be prevented or restored? 5. Pain (what is the incidence, how can we treat it?) and phantomvision (does this occur after enucleation in childhood? What is the incidence?)
Summary

Chapter 1 provides a short and general introduction on retinoblastoma. Retinoblastoma is the most frequent intra-ocular malignancy in childhood. Treatment involves either one or a combination of the following modalities: lasertherapy; cryotherapy; brachytherapy; chemotherapy (local or systemic); enucleation and external beam radiation therapy (EBRT). This thesis focuses on the outcome of Rb-patients treated with enucleation (and/or EBRT).

Currently the largest proportion of Rb-survivors has been treated by enucleation and/or EBRT. Although intra-arterial chemotherapy is a popular and promising alternative eye-sparing therapy, today this treatment method is particularly accessible in highly specialized centers in developed countries. Although no life-threatening complications are known, this therapy is not without risk and yet little is known about the long-term effects. Enucleation remains a very safe and effective treatment method feasible in every setting and will retain an important role in the treatment of advanced retinoblastoma especially in eyes where the possibility of useful vision after eye-sparing therapy is low. In addition to the efficiency, relatively low costs and short treatment period compared to eye-sparing therapy, enucleation has the advantage that material for histopathological examination is obtained. With histopathology the presence of risk factors for metastasis can be determined (if present requiring additional chemotherapy). Additionally, genetic testing of the tumour material - in combination with blood tests - can differentiate between heritable and non-heritable Rb, which is important in the counseling of patients and families. Patients with heritable Rb have an increased risk of second primary malignancies and their children have a 45% chance of developing retinoblastoma.

However, enucleation is an invasive and definitive procedure with the loss of a child’s eye. The functional and cosmetic result of enucleation in Rb-patients has received little attention so far.

The young age at enucleation and in some the additional treatment with EBRT and/or chemotherapy makes retinoblastoma patients a special group. In these young patients the orbit and skull is not yet fully grown. Nowadays, after an enucleation, the eye cavity is filled with an implant. Until the arrival of the MRI implants were withhold from the Rb-patient, because of the fear to miss recurrent tumours. An implant allows for some motility of the overlying artificial eye and for volume substitution. The surgeon strives for the best possible cosmetic result with the least chance of complications. Here, a distinction can be made between major complications such as extrusion of the implant with subsequent need for reconstructive surgery and minor complications such as insufficient volume substitution offering less cosmetic satisfaction. However, it is not clear which
implant material, -size and - shape and which surgical technique can best be used. There are many different possibilities and comparative studies are missing. Publications (largely from the United States) suggest a preference for integrated or porous implants (in which fibrovascular ingrowth is seen) over non-porous implants, because they would theoretically have a lower chance of extrusion and infection and they would facilitate a better motility of the artificial eye.

However, it was shown that non-pegged porous implants do not yield a better motility than non-porous implants. Studies proving lower extrusion and infection rates are lacking. In addition, a porous implant is a much more expensive option than some other choices of implants. Besides, if necessary the porous implant is very difficult to remove operatively.

In chapter 2 we present a retrospective chart study investigating the outcome of 224 enucleations in the Netherlands performed within the last 23 years. Within this large population, two major groups could be identified: patients who received a porous (hydroxyapatite) implant and patients with who received a non-porous (acrylic) implant. Two smaller groups did not receive an implant or had received another implant type (solid, non-spherical) in the past (the Allen implant). In this study, we compared the complication risks of these different implant types. Implant specific events (13.2%) were registered, which showed that implant exposure (4.6%) and extrusion (2.7%) were the most frequent complications. We found a more favourable outcome of scleral wrapped acrylic implants than of scleral wrapped hydroxyapatite implants. For all groups, there was an increased risk of exposure, extrusion or socket problems with additional chemotherapy and/or radiotherapy. The few complications in this study were comparable to other studies in which implants with donorsclera were used and shows that placing a primary implant wrapped in donorsclera after Rb enucleation is safe and effective.

Today, many different orbital implant types and various wrappings are used. Also there are several surgical techniques described in literature. It is not clear which materials and which techniques are best. In order to gain insight in which materials and techniques are currently favoured in other retinoblastoma centers, we conducted a worldwide survey. This study is presented in chapter 3. Fifty-eight surgeons from 32 different countries completed the survey. Worldwide, a total of no less than 41 different combinations of implant types, wrappings and suturing techniques of the muscles were identified. This illustrates the lack of consensus and the lack of evidence which method and material is best. Personal experience seemed to be the surgeon’s main motivation for choosing a specific method or material.

In chapter 4 we call for the return of the (non-porous) acrylic implant which seems to be forgotten since the introduction of the many alternative porous implants.
Ocular prosthesis motility is one key aspect of the cosmetic outcome of enucleation. Implant manufacturers, usually, promise superior motility capacity of their implant and subsequent ocular prosthesis. However, in order to measure and compare motility, a reproducible non-invasive and objective measurement method is required. Till present, such a tool, which can be easily applied on children, did not exist and thus objective comparison of various materials and methods was not feasible. In chapter 5 we introduce a new method using the iView X\textsuperscript{tm} Eyetracker with specialized software; the eyetracker locates the pupil using an infrared system. The position of the pupil is constantly measured by this system and expressed in numbers (coordinates). The patient looks at a figure on the computerscreen which moves from the left to right. The eye and artificial eye follow this horizontal movement and the numbers deriving from the infrared system are translated in a graph with amplitudes representing the eyemovement. The movement (i.e. motility) of the artificial eye can be expressed in a percentage of the movement of the healthy eye by comparing their amplitudes.

Our study population was operated at a young age. The size of the implant varies according to the size of the orbit at the time of surgery. Nowadays, the idea exists that larger implants provide better volume substitution with subsequent less residual ‘empty space’, resulting in a better translation of the movement onto the artificial eye. In this study we could not confirm this. Our measurements showed no significant difference of prosthetic eye motility comparing patients with small and large implants. We also found no difference in the motility of the non-porous acrylic implant and the porous hydroxyapatite implant.

As mentioned before, the current tendency is to place the largest possible implant believing this would result in best cosmesis. However, studies reporting the cosmetic outcomes of enucleation (and/or external radiation) are scarce. In chapter 6 we deal with cosmetic alterations and potential insufficienties (regarding volume, symmetry, eyelid positioning, artificial eye motility) as result of enucleation (and/or EBRT) in Rb-patients. Furthermore we inventorized the experience of pain and phantomvision. Phantom vision, the perception of images seen with a blind or absent eye, is a phenomenon described in adults. Whether this is also present in patients who have lost their eye during childhood has never been examined in a cohort and is only sporadically described in case reports. During a two year period we have approached the Dutch cohort of retinoblastoma survivors (treated by enucleation and/or EBRT) with questionnaires regarding satisfaction with the appearance and we have performed measurements on the eyes and eyelids. A total of 195 patients (40-88 years) participated, of which the majority (n = 131) had been treated with unilateral enucleation. Outcome parameters included: deviations of the upper and/or lower eyelid; volume
deficiency; orbit and eye lid aperture asymmetry; prosthesis motility; pain and
phantom vision and overall judgement by observer and patient. This study
demonstrated that the presence of an orbital implant improves the cosmetic
outcome in terms of prosthetic motility, superior sulcus depth and lower eyelid
position. The risk of ptosis increases with the use of larger implants. Moreover,
larger implants do not amend orbital symmetry, volume and prosthesis motility.
Although we could not report on any advantages when using the largest implant,
we did see significantly more frequent superior sulcus deficiencies in patients
with a small implant compared to a medium sized implant.

Treatment with EBRT gave unfavourable results. We documented socket
contraction, more volume deficiency and deep-set eyes. Also pain was experienced
more often. Of all patients 25% experienced pain in and around the eye or socket
(18% of the patients treated with enucleation and EBRT and 43% of the patients
only treated with EBRT). Pain on a daily base was experienced in 20%.

In our cohort, eleven patients reported to experience phantom vision. None
of them found it disturbing. The incidence in adults is reported much higher
(42%). The low number of patients developing phantomvision in our cohort can
be potentially explained by their young age at enucleation at which the visual
pathways are not yet fully developed.

Overall patients (and/or parents) were satisfied regarding the cosmetic result.
We (the observers) also scored fairly positive (cosmesis of 64.3% of all patients
were categorized as acceptable or good; within the category ‘good’ (29.7% of
total) the majority (85.2%) was treated by unilateral enucleation. Within this
treatment group, 62% of patients categorized as bad or poor was afflicted with a
ptosis. Additional treatment with EBRT had a negative effect on the cosmesis. In
more than half of the patients we found an opportunity for improvement by means
of a simple adjustment of the prosthesis or with a simple surgical procedure. In
children prosthesis adjustments are frequent necessary because of their orbital
and soft tissue growth. At this moment we are developing the application of
three-dimensional designing and printing of the prosthesis to facilitate a more
predictable and easy process for adaptation.

In Chapter 7 we discuss another problem that many patients face with an
artificial eye: irritation and discharge from the socket. In the clinic, irritation/infection
and discharge from the socket is a frequent reported problem. This problem has
gotten little attention in the literature. The cause of this problem and an adequate
management approach is unknown. In order to offer recommendations for
the management of this problem in the clinic, we studied the causes and their
treatment. Patients were questioned about their daily habits and hygiene regarding
the prosthesis and their experience of irritation, discharge and infection. Cultures of

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the sockets were taken in a subgroup to identify any pathogenic micro-organisms. In these cultures we identified bacteria mostly s. Aureus or h. Influenzae causing purulent hyperemic sockets. These infections were associated with younger age and with upper respiratory tract infection. There was no association found between complaints and cleaning habits of the prosthesis.

Our study reveals that irritation, mucoid or purulent socket discharge are frequently (≥ monthly) experienced in 75 (39.5%), 127 (66.8%) and 15 (13.2%) sockets respectively of 182 study participants. In symptomatic hyperaemic sockets, topical antibiotics can be prescribed; in non-responders, underlying pathologies – prosthetic, eyelid, orbital, lacrimal, other related problems or a combination of these- need to be identified to offer a suitable and targeted treatment. In chapter 7 we present a decision-tree which can help the clinician to identify the problem and suggests the concurrent treatment. Since we hypothesize that the experienced discomfort and amount of discharge would reduce with improvement of the tearfilm we start experimenting with prosthetic surface adaptations rendering hydrophilicity.

Another late postenucleation effect is persistent socket pain. This was reported in 17% of patient solely treated by enucleation in our cohort (presented in chapter 6). In a systematic review of the literature (chapter 8) we identified and tabulated causes and treatment modalities of postenucleation socket pain. It seems difficult to identify the source of the pain and it is presumably a multifactorial late effect. We recommend to perform a physical examination regarding the fit of the prosthesis (and presence of pain with and without the prosthesis in situ), the positioning of the eyelids, the tear film quality, the conjunctiva and socket (colour, exposure, swelling, papillae, contraction, symblephera, depth of fornices), discharge (extend and colour) and palpation of the orbit and pressure on the trochlea (induction of pain may be associated with trochleitis). Primary measures can be polishing of the prosthesis, adjustment of the prosthesis, treatment with lubricants or antibiotics, in case of pressure pain on the trochlea one can inject steroids, and in cases unresponsive to primary measures and apparent socketcontraction, implant exposure, symblephera or eyelid malpositioning surgery can be considered. Without an identifiable cause it can be defined as phantom pain. Treatment of persistent socket pain is controversial, but most reported -and frequent effective method- is removal of the implant and re-insertion of a dermis-fat graft.

In our case series (presented in chapter 9) we recognise that socket rehabilitation with dermis-fat implantation may also offer a convenient approach to other problems of the socket such as chronic infection of the socket, enophthalmos, deep superior sulcus deformity and lidmalpositioning.
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The healing and shape of the socket after the operation is subsequently decisive for the shape of the eye prosthesis. This thus affects the cosmetic result. Especially in complicated sockets in which a dermis-fat implant is inserted, it is important to control the shape of the socket during the healing process. For this purpose a temporary conformer must be placed. In chapter 10 we present a new type of conformer, custom designed through 3D planning and printing. This technique will facilitate a more simple translation into the design of an adequate prosthesis.