FRACTIONATED STEREOTACTIC RADIOTHERAPY FOR UVEAL MELANOMA

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FRACTIONATED STEREOTACTIC RADIOTHERAPY FOR UVEAL MELANOMA

Gefractioneerde stereotactische radiotherapie voor uveamelanomen

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Chapter 1

INTRODUCTION AND OUTLINE OF THE THESIS

Introduction

With an annual incidence of about 4 to 9 per million in the United States of America and European countries, uveal melanoma (UM) is a rather rare malignant disease entity [1]. UM can arise in any part of the uveal tract, that is in the iris, ciliary body and/or choroid. Iris melanomas are extremely uncommon and have a different nature as well as treatment approach. This thesis will only relate UM to choroidal and ciliary body melanomas, which take up 95% of all UM. Most the patients are diagnosed with UM because of having (mild) visual symptoms, such as blurred and/or declined vision, light flashes, metamorphopsia (change in shape of an object) and floaters ("floating flies"). Although effective local treatment options for the primary tumor, are available, a substantial part of the patients eventually die from metastatic disease. UM metastasize haematogenously, mainly to the liver. The diagnosis of metastatic uveal melanoma disease is often several years after the primary treatment, with a median of 4 to 6 years. Once (liver) metastases have been diagnosed, the prognosis is infaust in almost all cases with a mean survival of 3 to 9 months.

In 1978 Zimmerman, McLean and Foster suggested that enucleation, which was historically the gold standard treatment option, could possibly accelerate the dissemination of tumor cells, noting the abrupt rise of mortality rates two to three years post-enucleation[2]. This was the incentive to the development of eye sparing treatment modalities. Although they did not lead to better metastatic free survival rates, these modalities have taken an important place in the treatment of UM nowadays, because of advantages of the treatment, such as preservation of the affected eye and maintenance of a usable vision [3, 4].

Radiation therapy of choroideal melanomas was initiated in 1930 by Moore [5], who used radon seeds. Modern techniques of brachytherapy involve a shielded plaque containing radioactive isotopes, sutured to the sclera. Meanwhile, brachytherapy has proven to be a good alternative for enucleation with excellent local control rates, especially for small and medium sized tumors [6] [7-11]. Heavy particle irradiation is used to treat medium sized and large UM [12-17]. Nowadays, UM has become one of the accepted indications for treatment with heavy particles. The advantage of this technique is the precise dose delivery and the rapid dose fall off due to the Bragg peak characteristics. Moreover, there is no maximum limit regarding the tumor thickness.

Both the size and the location of these (often large sized) UM make these tumors highly suitable for this type of irradiation. The results in terms of local control have proven to be very good, with local control rates above the 90 percent [14-21]. However, the secondary enucleation rate due to toxicity or local failure is still substantial, i.e. 6 to 25 percent [12, 17, 18]. This is mainly caused by the appearance of neovascular glaucoma. Treatment by heavy particle accelerators are extremely costly, and consequently, the facilities for this type of treatment are scarce. Fortunately, currently there are new initiatives, also in the Netherlands. Photon accelerators, on the other hand are widely available and cost-effective. It is therefore appropriate to find out whether UM could be irradiated with photons. That is, with a control rate comparable to protons and a very low complication probability. The eye consists of (surrounding) healthy structures which are very sensitive to radiation. The advent of precise irradiation techniques, such as stereotactic radiation therapy (SRT), make it possible to irradiate the tumour and spare the surrounding tissue to a great extent [22-29] [30, 31]. For UM a radio surgical technique (single fraction SRT) has been introduced in 1987 with good results regarding local control. However, the number of significant radiation induced adverse reactions was high (13 out of 14 patients) [24]. By fractionating the dose, normal tissue can be spared even more.

The **aim** of this thesis is to describe an accurate and reproducible method for the fractionated stereotactic treatment (fSRT) of uveal melanoma and to investigate its safety, efficacy, and complications in short term and long term follow-up. This chapter presents an overview of the problems at stake. A number of relevant aspects with respect to fSRT of UM are described in the following chapters (2-6):

Prerequisite of fSRT is the accurate reproducibility of the position of the tumor during treatment. In **chapter 2** the development of a non-invasive, reliable, patient friendly relocatable stereotactic frame with an eye fixation module for irradiation of eye melanoma is described. Also, the repositioning accuracy of this relocatable frame was evaluated.

In **chapter 3** early data on the effectiveness and acute side effects of fSRT for uveal melanoma are reported.

The local control at long term, late side effects and survival of uveal melanoma patients treated with fSRT are reported in **chapter 4**.

Irradiation of the lacrimal gland can result in atrophy causing reduced tear production and consequently, a dry eye. When applied to the whole organ, a clear dose effect relationship has been established. Using conformal irradiation techniques such as fSRT, the surrounding tissues such as the lacrimal gland can be partly spared. **Chapter 5** describes the analysis of a dose volume effect for (inhomogeneous) irradiated lacrimal glands.

In ocular oncology centers more than one treatment facilitity is available and the choice for treatment is made based on the clinical history, ophthalmic examination and tumor data. However, for a substantial part of medium sized UM different treatment options are available. Beside enucleation, medium sized UM could be treated with different radiation modalities, i.e. brachytherapy, fSRT and proton therapy. Out of literature, it is difficult to compare the outcomes of these modalities, since most publications are based upon retrospective studies. Moreover, comparative survival studies of brachytherapy versus SRT have not been published yet. In **chapter 6** we studied overall survival, metastatic-free survival and secondary enucleation rate of choroidal melanomas treated with Ruthenium brachytherapy (Ru-106) versus stereotactic radiotherapy (fSRT) of patients with interchangeable characteristics. The main goal of our study was to determine the differences in clinical and survival outcome comparing Ru-106 and SRT for UM of comparable dimensions.

In **chapter 7**, a summary of the relevant publications is listed. Also future perspectives are discussed.

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Chapter 2

A MODIFIED STEREOTACTIC FRAME FOR UVEAL MELANOMA

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Abstract

Purpose

To describe a reliable, patient friendly relocatable stereotactic frame for irradiation of eye melanoma and to evaluate the repositioning accuracy of the stereotactic treatment.

Methods and materials

An extra construction with a blinking light and a camera is attached to a non-invasive relocatable Gill Thomas Cosman stereotactic frame. The position of the blinking light is in front of the unaffected eye and can be adjusted to achieve an optimal position for irradiation. The position of the diseased eye is monitored with a small camera. A planning CT scan is performed with the affected eye in treatment position and is matched with a MR scan in order to improve the accuracy of the delineation of the tumor. Both the translation and rotation of the affected eye are calculated by comparing the planning CT scan with a control CT scan, performed after the radiation therapy is completed.

Results

Nineteen irradiated eye melanoma patients were analyzed. All patients received 5 fractions of 10 Gy within 5 days. The DCH (depth-confirmation helmet) measurements of the day-to-day treatment position of the skull within the GTC frame were analyzed in anteroposterior, lateral and vertical direction and were 0.1±0.3, 0.0±0.2 and 0.2±0.2 mm (mean±sd), respectively. The average of translations of the eye on the planning and control CT scan were 0.1±0.3 mm, 0.1± 0.4 and 0.1±0.5 mm, respectively. The median rotation of the diseased eye was 8.3 degrees.

Conclusions

The described Rotterdam eye fixation system turned out to be a feasible, reliable and patient-friendly system.

Introduction

In adults melanoma is the most common malignancy of the eye and arises from the uvea, formed by the choroid, ciliary body and iris. Uveal melanomas have traditionally been treated by enucleation. Other treatment options use radiotherapy with or without transpupillar thermotherapy. Recent comparative studies showed no difference in survival between enucleation and Co-60 plaque radiation therapy [1] or I-125 brachytherapy [2]. Thus, brachytherapy appears to be a useful alternative for the treatment of small uveal melanoma. Proton and Helium radiation techniques are also widely used, particularly in medium sized tumors [3-9].

Radiosurgery (a high radiation dose in 1 (to 3) fractions) of eye melanoma began in 1987 using the Gamma Knife, with as major advantage the very precise delivery of dose to the tumor [10-13]. Local control rates of 93% to 98% were achieved. Due to the high single dose, the most important disadvantage of radiosurgery is the loss of radiobiological sparing if critical structures are adjacent to the tumor, resulting in an enhanced complication probability [10, 13-15]. Moreover, the invasive frame as applied with radiosurgery is rather uncomfortable for patients and not suitable in case of fractionated treatment schemes. Fractionated stereotactic radiotherapy (fr. SRT) with a relocatable frame allows for delivery of an equivalent effective dose to the tumor combined with reduced effective dose in the surrounding tissues. The relocatable frame being non-invasive is also more convenient for patients. Finally, the repositioning accuracy (RA) of the relocatable stereotactic frame has shown to be sufficient [16]. However, the RA of the relocatable stereotactic frame does not imply the immobilization of eye movements. Fixation of the affected eye in a specified position can contribute to an even better sparing of critical structures. Several eye fixation methods have been developed, each with its specific disadvantages.

The ultimate challenge remains to design a method for fixation of the affected eye in a favourable treatment position during the whole course of fr. SRT of eye melanoma. The aim of this paper is to describe a patient friendly eye fixation device, attached on a relocatable stereotactic frame for eye melanoma patients and to analyze the RA of the target volume.

Methods and Materials

The eye melanoma stereotactic frame

For the purpose of stereotactic irradiation of eye melanoma the Gill Thomass Cosman frame (GTC frame™, Radionics, Burlington, USA) was modified [16, 17].

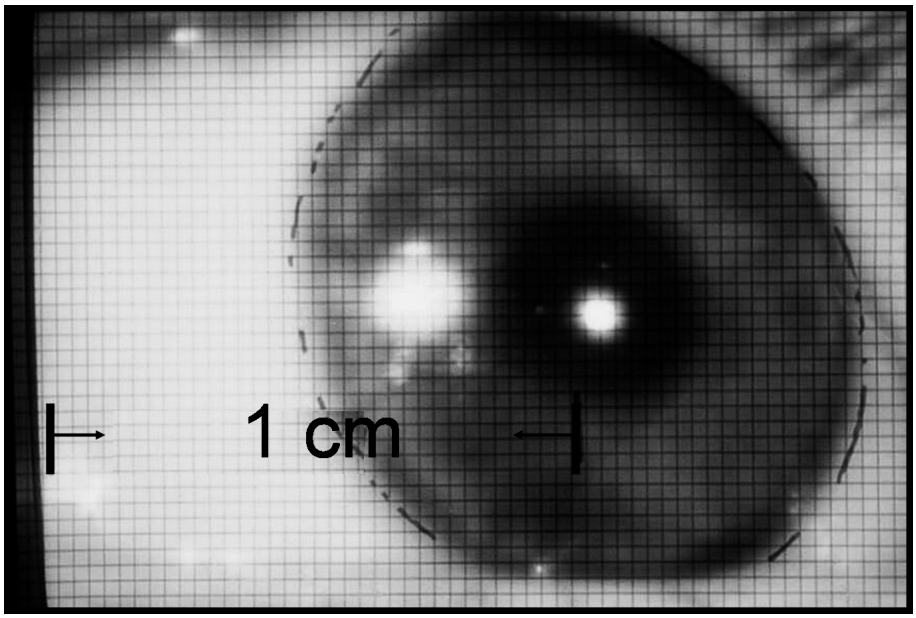
To immobilize the affected eye during the planning CT scan procedure and during the stereotactic irradiation in the intended treatment position, we used a plastic (PVC™) eye fixation device attached to the GTC frame, which contains both a blinking light and a camera (figure 1). The blinking light (fibre-glass connected to LED*)* is positioned in front of the healthy eye at a distance of 20 cm and its location can be changed in horizontal and vertical direction. The patient is asked to gaze at the blinking light. The position of the blinking light is adjusted to each individual patient in order to achieve an optimal angle of view; a small rotation of the eye-ball and tumor may improve tumor coverage and reduce the exposure to critical surrounding structures. A small camera, also fixed at the PVC attachment, is positioned at a distance of 20 cm from the affected eye to verify the position of the eye (i.e. the angle of view) by checking the circumference of the iris and pupil, drawn on an overhead sheet at the monitor screen (figure 2). In order to quantify the rotation of the eye, a scale strip is recorded by the camera and contoured on the sheet.

Patients

Twenty-three patients were treated with fr. SRT between 1999 and 2002. Of each patient a planning CT scan and a control CT scan (after treatment) were made. Four patients had to be excluded: two control scans could not be analyzed for technical reasons and of a third patient the localizer frame was not placed on the GTC frame during the control scan. One patient did not look at the blinking light during the second CT scan (after completion of the radiotherapy series). Of the remaining nineteen patients, both the planning and control CT scan were available for evaluation of the modified frame and analysis of the repositioning accuracy.

FIGURE 1 *Relocatable stereotactic eye melanoma frame*

FIGURE 2 *Example of monitored eye; the contours of iris, pupil, eyelids and scale strip are drawn on the screen of the monitor and are used during radiation.*



Planning and treatment

MRI scan

Preceding treatment planning, a MRI scan (1,5 Tesla; axial and sagital T1w SE 3 mm-slices, and occasionally axial T2w TSE 3mm- slices) is made of the orbit of the affected eye.

Planning CT scan

Two planning CT scans are performed (AcQSim, Philips™) with the localizer frame positioned on the GTC frame. The first scan is made of the whole skull. A second scan with contrast (Omnipaque®) at the level of the eyes is performed with the affected eye in treatment position recorded by the camera (1.5-mm slices with an index of 1 mm). From the second scan, two fields of view are reconstructed: one containing the rods of the localizer frame, the second reconstruction enclosing the orbit of the diseased eye. The sizes and centers of the fields of view are recorded.

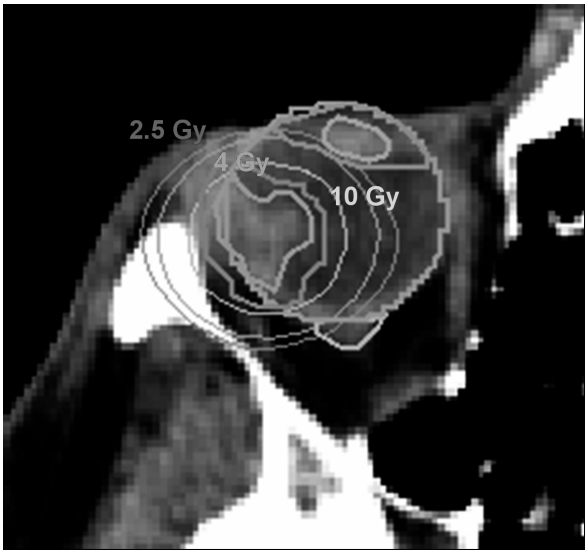
Contouring

The CT scan of the orbit is matched with the MRI-scan in order to improve the accuracy of delineation of the GTV, using ImageFusion™ Version 2.02 (Radionics). The primary lesion is contoured on both the CT scan and the fused MRI. The GTV encloses the primary lesion contoured on CT, corrected for any extension of the visible lesion as observed on MRI, and taking into account the findings of ultrasound imaging and fundus photography. Besides the GTV, the critical structures are also contoured on CT, i.e. the optic nerves and the lens with ciliary body of the affected eye and the contralateral eye. The contours are transferred into the whole skull CT scan using an in-house developed software program.

Planning

The PTV is constructed by adding a 3 dimensional margin of 2 mm to the GTV. A treatment plan is made using stereotactic arcs of 6 MV photons (XKnife RT™ 1.03, Radionics), with one or more isocenters. A total dose of 50 Gy in 5 fractions is prescribed to the 80 % isodose surface, encompassing the PTV. Doses of 4 Gy per fraction in the optic nerve and 2.5 Gy per fraction to one-fourth of the lens and ciliary body are considered to be acceptable. An example of treatment planning is shown in figure 3.

FIGURE 3 *Example of treatment planning; the eye, GTV, PTV, lens, ciliary body and optic nerve are contoured. The isodose lines presented are 10, 4 and 2.5 Gy per fraction.*



Treatment

The total dose is delivered on 5 consecutive days, i.e. Monday to Friday. Before each treatment the position of the skull within the GTC frame is checked by DCH measurements. Retrospectively, the data of these measurements are analyzed with a spreadsheet program (Excel™), designed for this purpose. The DCH measurements were split into a displacement in anteroposterior (AP), lateral and vertical direction. The position and movements of the diseased eye are monitored with the on-line video camera. If the eye moves more than 2 mm with regard to the initial drawing of the eye and lens, the irradiation is interrupted and the patient is instructed to gaze at the light again.

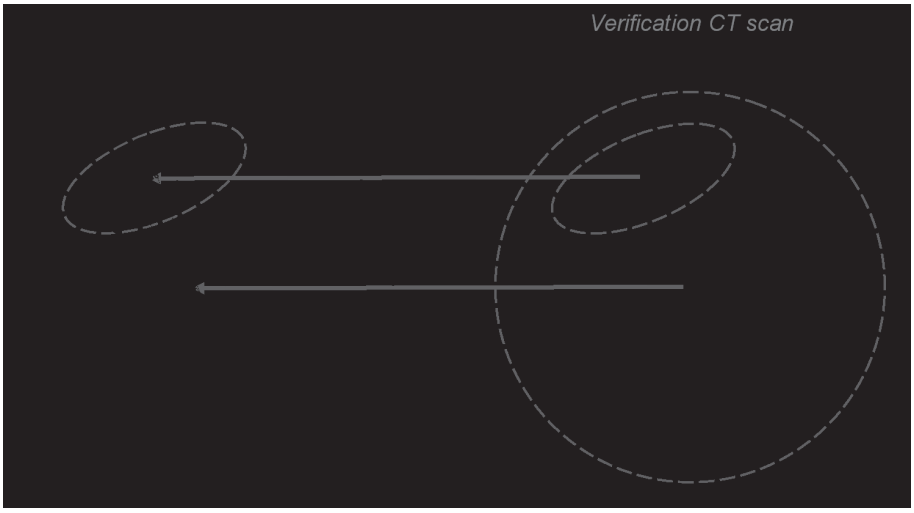
Verification of the fixation of the eye

After the last fraction, a second CT scan in treatment position is performed. The eye and lens are delineated on the planning and control CT scan by the same clinician.

Differences in eye position, relative to the localizer frame, can be described in translations and rotations of the eye-ball. Since the tumor is not always clearly visible on CT, its coordinates could not be used reliably for calculation of the rotation. However, the distance between the tumor and the center of the eye is approximately the distance between the lens and the center of the eye. Therefore, for determination of the rotation, both the coordinates of the eye and the lens are used as depicted in figure 4. The translation of the eye is defined as the shift of the center of the eye on the CT scans. The coordinates of the lens of the second scan are corrected for the translation of the eye (depicted by vector *n*). The distance between the coordinates of the lens and the eye of the planning scan is called vector *p*; vector *q* is the distance between the corrected coordinates of the lens of the second scan and the coordinates of the lens of the planning scan. The rotation of the eye is defined by the angle (α) between the vectors of the center of the eye to the center of the lens on planning CT scan and to the center of the lens on the control CT scan, corrected for the translation of the eye (i.e. the angle between vector *p* and *q*), using equation 1:

$$\alpha = 2 \cdot \sin\text{-}1(q/2p) \qquad \textbf{(1)}$$

FIGURE 4 *Schematic view of rotation calculations; the contours of the control scan are striped; the center of the lens of the control CT scan is corrected for the translation of the eye (n). The translation of the lens (q) is calculated by subtracting the coordinates of the corrected center of the lens from the coordinates of the center of the lens on the planning CT scan; p is the distance between the center of the eye and the center of the lens. The angle of rotation is depicted by α.*



Statistical analysis

Since the results of the translation did not show a normal distribution, the mean and standard deviation are of limited value. Instead, we used the median and range for our analysis. For the range, the maximum and minimum of all results were used. A possible correlation between gaze direction of the eye and the deviation of rotation was tested using the Spearman's test.

As stated, the DCH measurements were split into displacements in anteroposterior (AP), lateral (LAT) and vertical (VERT) direction. The means of the AP, lateral and vertical displacements of a particular fraction are considered to be the estimate of the shift in this direction. The mean of these values of all fractions is the systematic error, while the random error is the standard deviation of the variations of the shifts.

Results

Tumor data

All 19 patients received 5 fractions of 10 Gy on the primary lesion. The general data of this group is pointed out in Table1.

TABLE 1 *General Data*

Characteristics	Mean	SD	N[a]
Age *(years)*	61	10	
Size *(mm)*			
Diameter			
Horizontal	10.8	2.6	
Vertical	9.6	2.6	
Prominence	5.4	2.1	
Site			
Nasal			6
Central			7
Temporal			6

[a] Total number of patients is 19

Depth-Confirmation Helmet Measurements

The results of the DCH measurement are summarized in Table 2. The systematic errors are 0.1±0.3, 0.0±0.2 and 0.2±0.2 mm, in anteroposterior, lateral and vertical direction, respectively. The mean random (i.e. daily) displacements are 0.4, 0.5 and 0.4 mm, respectively.

TABLE 2 *Depth-Confirmation Helmet measurements (Planning CT and daily measurements)*

	Systematic error [a] *(mm)*	Random error [b] *(mm)*	Range *(mm)*
AP	0.1 ± 0.3	0.4	-0.7 – 1.4
LAT	0.0 ± 0.2	0.5	-1.0 – 1.0
VERT	0.2 ± 0.2	0.4	-0.2 – 0.9

[a] The systematic error is the mean of the mean shift of all patients (plus standard deviation)
[b] The random error is the standard deviation of the variations of the shifts

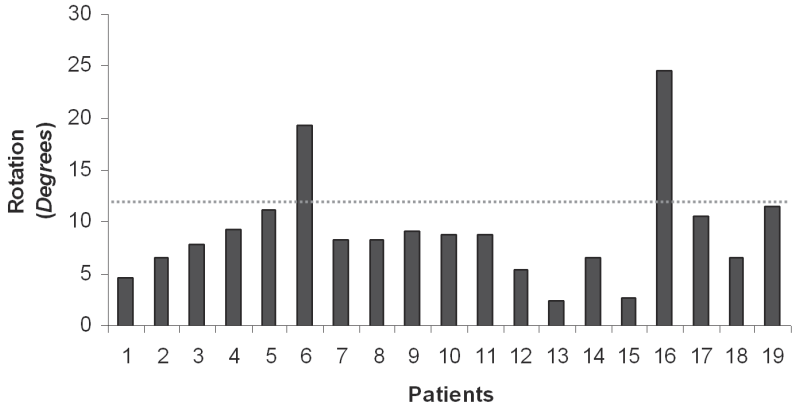
Comparison of CT scans

The mean errors of the DCH-measurements between the planning and control CT scans were 0.1±0.3 mm, 0.1± 0.4 and 0.1±0.5 mm for the AP, lateral and vertical direction, respectively.

The results of the translation of the eye and lens are presented in Table 3. The median translation of the eye was 0.5, 0.3 and 1.2 mm (in AP, lateral and vertical direction, respectively), with a range of 4.5 mm.

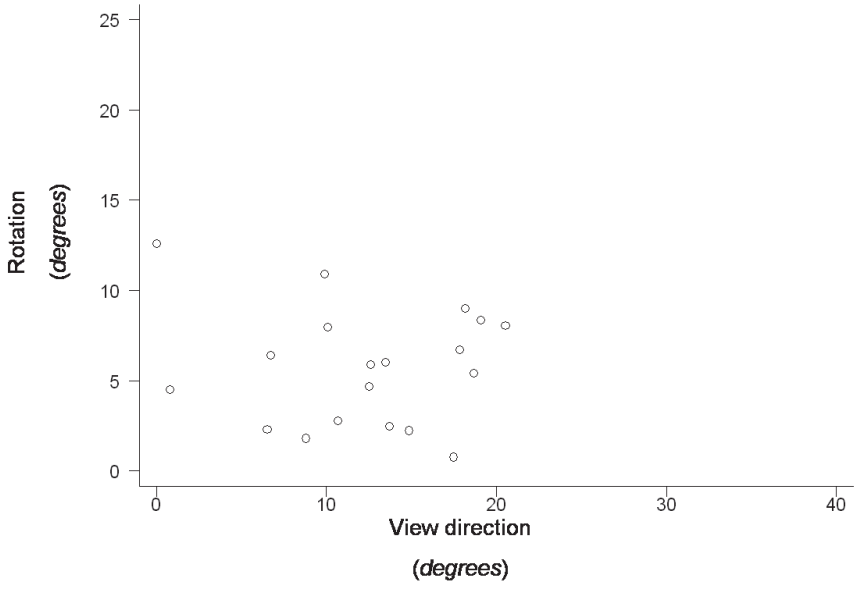
The median rotation of the eye was 8 degrees, with an inter-patient range of 22 degrees (Figure 5).

FIGURE 5 *Rotation of the eye per patient. The bars indicate the rotation of each patient; the dotted line is the maximum allowed rotation (see text).*

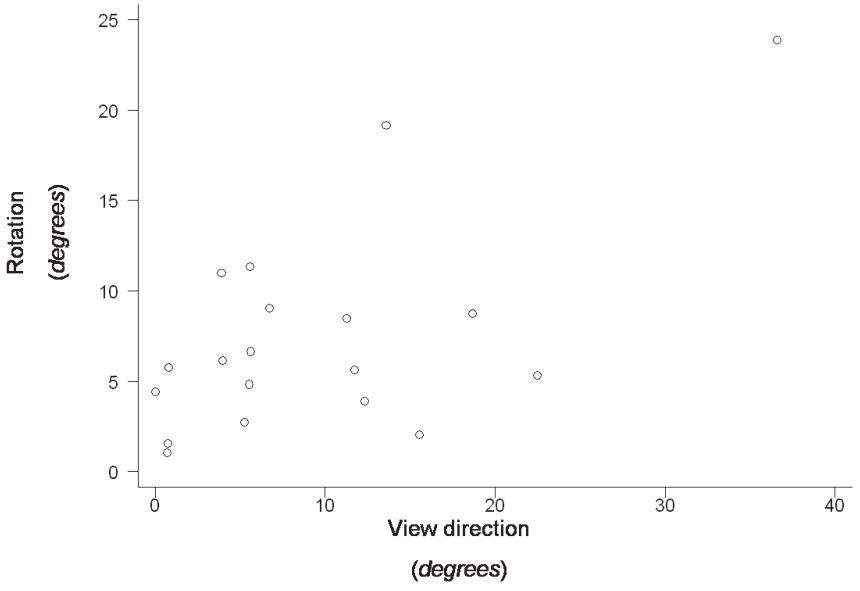


Although a comfortable gaze direction (straightforward) for each patient is the first intention, sometimes a forced gaze direction is required to spare critical structures. No statistical correlation between the rotation lens and angle of view direction was found (Figure 6).

FIGURE 6 *Correlation view direction and magnitude of deviation of rotation; the correlation of the gaze direction of the eye and the deviation of rotation was tested using the Spearman's test.*
a. Lateral direction; Spearman's rho of 0.098 (p=0.69)



b. Vertical direction; Spearman's rho of 0.397 (p=0.09)



Discussion

The clinical outcome of enucleation has been studied by several investigators [18-22]. It was suggested that there could be an enhanced dissemination of tumor cells caused by enucleation. Various eye sparing treatment modalities have been developed with the main goal of leaving the affected eye unimpaired with an optimal sparing of the visual function.

Stereotactic radiation therapy has proven to be a useful treatment modality for small, well localized tumors among which brain tumors, because of a very precise dose delivery with a rapid dose fall-off. In this respect, the design of immobilization techniques to fixate the position of the diseased eye has become of paramount importance. Since the introduction of eye sparing external beam radiation therapy in eye melanoma patients, several eye fixation methods have been described. In proton beam irradiation, patients were asked to focus on a light, while the gaze direction of the eye was checked by the position of the radiopaque tantalum rings on a film [8, 9]. Gragoudas et al. described a voluntary fixation of the eye that could be controlled throughout the procedure by monitoring the eye using a television system [23]. Using helium ion radiotherapy, Castro et al. described a technique in which the fixated eye was checked by close-up monitoring by a camera [3].

Zehetmayer et al. described a suction fixation method for radiosurgical treatment of eye melanomas [24-26]. After retrobulbar anaesthesia, a circular vacuum chamber fixes the eye, similar to fixation techniques used for corneal surgical procedures. The vacuum chamber is linked to the stereotactic frame. In patients treated by Mueller et al. complete akinesia of the eye was achieved by retrobulbar anaesthesia [11, 27]. Langmann et al. anaesthetized the insertions of the four rectus muscles transconjunctivally, by a retrobulbar anaesthetic block. [12].

Being invasive, these accurate fixation systems, however, are not ideal for fractionated stereotactic radiation therapy. Moreover, a non-invasive fixation system is more comfortable for patients. Only few authors describe an eye fixation method for fr. SRT [28-30]. Bellmann et al. described a method in which patients are instructed to look at a fixation point with their diseased eye [30]. Since most patients have a declined visibility due to the tumor and because of the conjugated eye movements, it seems more reliable to make use of the vision of the healthy, while monitoring the movements of the diseased eye. In the immobilization technique described by Dieckman et al. [28],

the fixation point is not movable, so patients have to look straight forward. Since in some instances a different direction of the eye can result in more sparing of critical structures, a non-movable fixation point does have implicit limitations. Moreover, the RA was only analyzed using the eye movements as monitored by the camera. This is less suitable, because of the lack of a reliable reference point, since the camera could move as well. Tokuuye et al. used no stereotactic frame [29]. Patients were simply instructed to look forward; a plastic head mould supported the eye fixation.

The eye fixation system for fr. SRT presented in this paper has an adjustable fixation light placed in front of the healthy eye, so that the gaze direction of the eyes can be changed in order to get an optimal position of both the target and critical structures for optimal irradiation. The position of the diseased eye is monitored during CT scanning as well as during treatment. Displacements of the eye relative to the contour on the monitor screen at the time of radiotherapy can be due to either a shift of the head in the GTC frame (although within the allowed 2 mm) or the rotation of the eyes. To minimize the effect of the shift of the head, the fixation light as well as the camera is positioned as far from the eyes as possible. The distance is limited due the size of the gantry aperture of the CT scan and the rigidity of the material used for fixation. The daily set-up deviations are acquired by the use of DCH measurements, which yield a day-to-day deviation of the head position inside the GTC frame. The variations are comparable with previously reported results of repositioning accuracy of the GTC frame in literature [16, 17]. The results of DCH measurements are comparable to the CT scan measurements and are clearly within the error permitted during treatment, i.e. the median translation of the eye was 0.5, 0.3 and 1.2 mm in AP, lateral and vertical direction, respectively. However, the range of the translation was considerable (Table 3). One patient showed unexplainable large deviations of more than 2 mm.

The consequences of the eye movements on the accuracy of irradiation of the tumor were calculated. Since the mean distance between the center of the eye and the center of the GTV is 9.5 mm, a rotation of 12 degrees will result in a shift of 2 mm (which is the GTV-PTV margin). Two patients had rotations larger than 12 degrees (Figure 5).

The method of the individual adjusted fixation light is feasible, since there was no correlation between the gaze direction and the magnitude of rotation deviation.

Improvements of the Rotterdam eye fixation system with respect to rigidity and MRI compatibility are warranted. Furthermore, a reliable QA device for the eye fixation system is in development.

TABLE 3 *Results Translation (mm)*

	Eye		Lens	
	Median	**Range**	**Median**	**Range**
AP	0.5	(0.1 – 1.8)	0.4	(0.0 – 1.6)
LAT	0.3	(0.0 – 4.5)	0.4	(0.1 – 5.3)
VERT	1.2	(0.0 – 3.9)	0.6	(0.1 – 2.8)

Conclusion

The Rotterdam eye fixation system appeared feasible and reliable and is very patient-friendly. Some improvements of the frame are warranted.
The daily DCH-measurements combined with the eye fixation are sufficient RA check-up for treatment.

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Chapter 3

EFFECTIVENESS OF FRACTIONATED STEREOTACTIC RADIOTHERAPY FOR UVEAL MELANOMA

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Abstract

Purpose

To study the effectiveness and acute side effects of fractionated Stereotactic Radiation Therapy (fSRT) for uveal melanoma.

Methods and Materials

Between 1999 and 2003, 38 patients (21 male, 17 female) were included in a prospective, nonrandomized clinical trial (mean FU of 25 months). A total dose of 50 Gy was given in 5 consecutive days. A blinking light and a camera (to monitor the position of the diseased eye) were fixed to a non-invasive relocatable stereotactic frame. Primary endpoints were local control, best corrected visual acuity (BCVA) and toxicity at 3, 6, 12 and 24 months, respectively.

Results

After 3 months (38 patients) the local control was 100%, after 12 months (32 patients) and 24 months (15 patients) no recurrences were seen. The BCVA declined from a mean of 0.21 at diagnosis to 0.06 two years after therapy. The acute side effects after 3 months were: conjunctival symptoms (10), loss of lashes or hair (6), visual symptoms (5), fatigue (5), dry eye (1), cataract (1), and pain (4). One eye was enucleated at 2 months after fSRT.

Conclusions

Preliminary results demonstrate that fSRT is an effective and safe treatment modality for uveal melanoma with an excellent local control and mild acute side effects. The follow-up should be prolonged to study both local control at long-term and late toxicity.

Introduction

In adults, uveal melanoma is the most common primary intraocular malignancy. Distant metastases will occur in about fifty percent of the cases with a maximum death rate at two to three years after the primary diagnosis. Uveal melanoma has traditionally been treated by enucleation of the tumor-containing eye. From 1970 on, various eye sparing treatment modalities have been developed with as aim an optimal sparing of visual function. Nowadays, for small and medium sized uveal melanomas radiotherapy has become the first choice of treatment. Brachytherapy appears to be a good alternative for enucleation in the treatment of small uveal melanoma, according to recent comparative studies [1, 2]. For medium sized tumors, proton beam and helium ion radiation techniques are widely used [3-9]. Radiosurgery for uveal melanomas has been introduced in 1987 with excellent results of local control [10-13]. However, the most important disadvantage of single fraction high dose radiosurgery is an enhanced complication probability, which causes the loss of radiobiological sparing if critical structures are adjacent to the tumor [10, 13-15]. Moreover, the invasive frame as applied with radiosurgery is rather uncomfortable for patients and less suitable for fractionated treatment schemes. Fractionated stereotactic radiotherapy (by the use of a linear accelerator (LINAC)) reduces the effective dose in the surrounding tissues with a delivery of an equivalent effective dose to the tumor. The relocatable frame being non-invasive is also more convenient for patients. A longitudinal cohort study has been initiated in our clinic in order to study both the effectiveness and the safety of this treatment modality. Patients with uveal melanoma are being treated by fractionated LINAC-based stereotactic radiation therapy (fSRT), following a standard treatment protocol.

Methods and Materials

Study design

This report evaluates the safety and efficacy of fSRT for uveal melanomas by describing the results of the first 38 patients treated in a prospective, consecutive series, one-center clinical study. This trial will continue and patients will be followed for 10 years to study late side effects and melanoma-related death. For this study approval was obtained from the Institutional Review Board at this institution. All patients are informed about the different treatment modalities and signed an informed consent.

All consecutive patients with uveal melanoma of choroid or ciliary body smaller than 12 mm of thickness and 16 mm of diameter were included. Patients were treated if all criteria for head and eye fixation were within fixed limits. Patients should be at least 18 years with a WHO performance status of 0-1. They were excluded if there was clinical evidence for metastatic disease.

Patients

Between 1999 and 2003, 38 uveal melanoma patients (21 male, 17 female) with a mean age of 61 years were included into the study (Table 1). At diagnosis, thirty-six patients had visual symptoms, including a declined vision in 27 patients, light flashes, metamorphopsia (change in shape of an object) and floaters ("floating flies") in 11 patients, cataract in two and vitreous hemorrhage in another two patients.

TABLE 1 *General Data and Tumor Characteristics*

Characteristics	Mean	SD	N[a]
Age *(years)*	61		
Gender			
Male			21
Female			17
Size *(mm)*			
Diameter			
Horizontal	11.1	2.3	
Vertical	10.0	2.3	
Prominence	6.4	2.6	
Shape			
Dome			26
Mushroom			12
Location			
Anterior [1]			20
Posterior			17
Ciliary body			1
Distance to critical structures *(mm)*			
Fovea	3.6	3.1	
Papil	4.1	3.0	
Visual Acuity [2]	0.21	0.17	

[a] Total number of patients is 38
[1] Ora serrata and equator
[2] Visual acuity before treatment of affected eye

Pre-irradiation assessment

All patients were examined at the ocular-oncology clinic (G. Luyten), which included a full ophthalmologic examination and A and/ or B-scan ultrasonography. In specific cases fluorescence angiography was performed to confirm the diagnosis and / or to establish tumor progression. All patients had a complete physical examination before SRT, a chest X-ray, liver function tests and liver ultrasonography.

Tumor data

The prominence of the tumors varied between 2.2-11 mm, with a mean size of 6.4 mm; the mean diameter was 10 mm in horizontal and 11 mm in vertical direction (Table 1). The mean distance of the tumor to critical structures was 3.6 mm and 4.1 mm for the fovea and optic nerve respectively. About half of the tumors was located anteriorly, including one ciliary body melanoma, the other half at the posterior pole (Table 1 and 2).

TABLE 2 *Tumor Location (number of patients)*

	Nasal	Central	Temporal
Cranial	5	8	7
Central	0	3	5
Caudal	3	3	4

The uveal melanoma stereotactic frame

For the purpose of stereotactic irradiation of uveal melanoma, an extra construction, with a blinking light in front of the unaffected eye and a camera positioned in front of the diseased eye, was attached to a non-invasive relocatable Gill Thomas Cosman stereotactic frame (GTC frame™, Radionics, Burlington, USA) [16, 17]. The position of the blinking light can be adjusted to achieve an optimal position of the affected eye for irradiation. More detailed information about the Rotterdam eye fixation system is published previously [18].

Planning and treatment

Preceding treatment planning, a MRI scan (1.5 Tesla; axial and sagital T1w SE 1 and 3 mm-slices, and occasionally axial T2w TSE 3mm- slices) was made of the orbit of the affected eye. A planning CT scan with contrast (Omnipaque®) was performed (AcQSim, Philips™) with the localizer frame positioned on the GTC frame and with the affected eye in treatment position recorded by the camera (1.5-mm slices with an index of 1 mm). The intended position of the eye was recorded by a snapshot on which the circumferences of the eye, iris and pupil were drawn; these circumferences were used for verification of the intended position of the eye during treatment. Both scans were matched in order to improve the accuracy of delineation of the gross tumor volume (GTV), using ImageFusion™ Version 2.02 (Radionics). The GTV enclosed the primary lesion contoured on CT, corrected for any extension of the visible lesion as observed on MRI and taking into account the findings of ultrasound imaging and fundus photography. Also, the critical structures were delineated on CT, i.e. the lens with ciliary body of the affected eye, the contralateral eye and the optic nerves. The planning target volume (PTV) was constructed by adding a 3 dimensional margin of 2 mm to the GTV. A treatment plan was made using stereotactic arcs of 6 MV photons (XKnife RT™ 1.03, Radionics), with one or more isocenters (Figure 1). A total dose of 50 Gy in 5 fractions was prescribed to the 80 % isodose surface, encompassing the PTV. Doses of 4 Gy per fraction in the optic nerve and 2.5 Gy per fraction to maximal one-fourth of the volume of the lens and ciliary body were considered to be acceptable accepted doses.

All patients received 50 Gy in 5 consecutive days, i.e. from Monday to Friday. Before each treatment the position of the skull within the GTC frame was checked by depth confirmation helmet (DCH) measurements, as described in a former article [18]. The affected eye was immobilized during the stereotactic irradiation in the intended treatment position by means of the eye fixation device as described above and was monitored by the camera during irradiation (Figure 2).

Follow-up

After irradiation, patients were examined according to the protocol after six weeks, followed by a three monthly evaluation during the first two years; after two years the examinations were every four months. The follow-up program included ophthalmoscopy of the tumor-containing eye and the contralateral eye, measurement of the intraocular pressure, split lamp examination and B-scan ultrasonography of the affected eye.

The mean follow-up was 25 months, with a range of 10 to 36 months. No patients were lost to follow-up.

FIGURE 1 *Example of treatment planning; 3D view of right eye from anterior position The inset is the eye without beams: The tumor is indicated by an arrow; other structures are the lens and ciliary body, optic nerve, lacrimal gland and eyeball. For this planning, 5 arcs were used.*

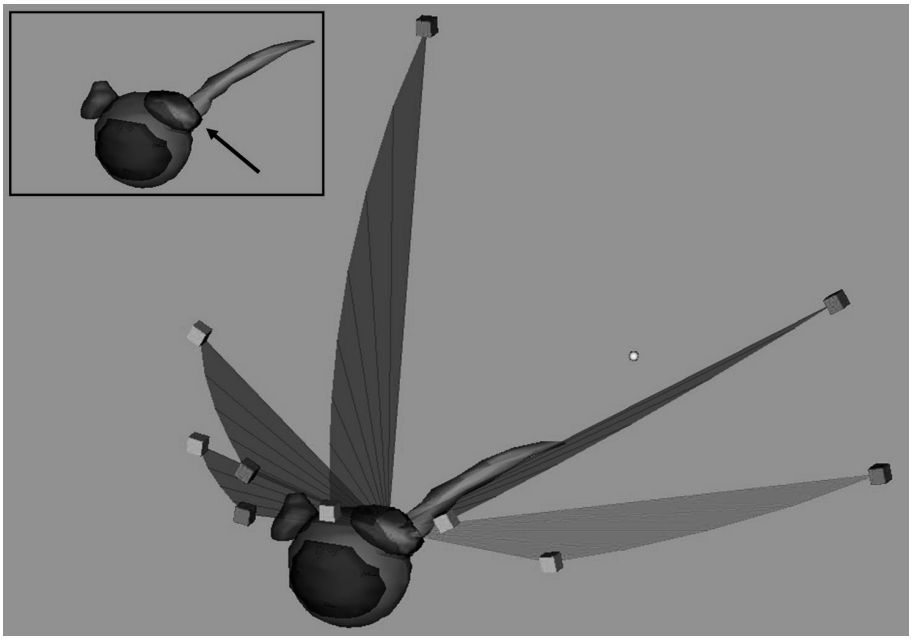
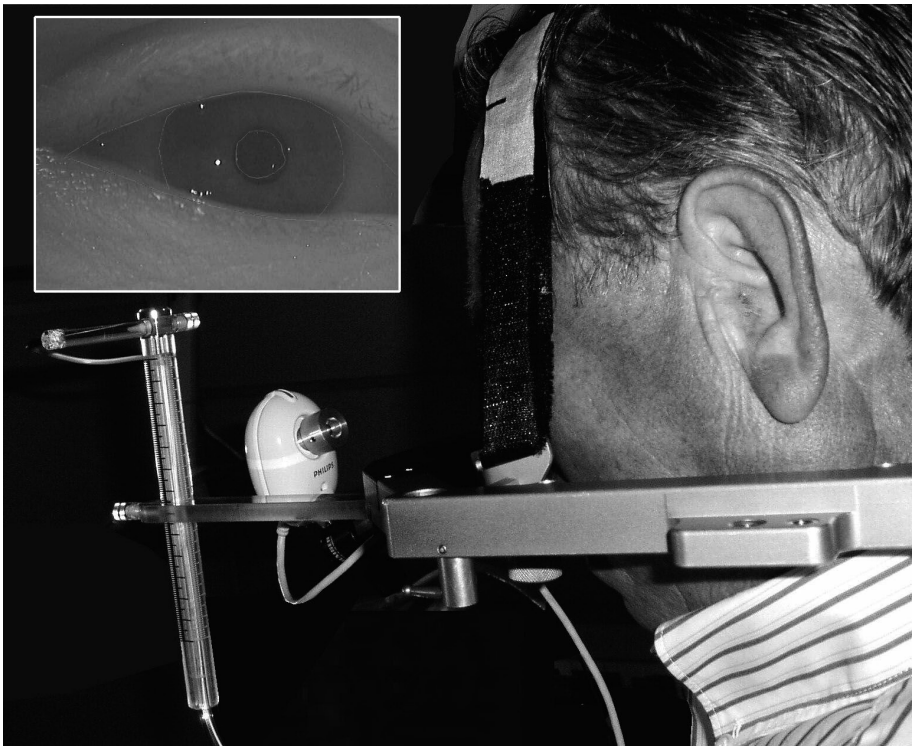


FIGURE 2 *Treatment of patient*
Patient gazes at the blinking light and a camera monitors the diseased eye.



Analysis

Endpoints

The primary endpoints are the acute toxicity after 3 months and local control after 3 months, 1 and 2 years, respectively. The secondary endpoints are the survival after 5 and 10 years.

Definition of local control and response

Local control is defined as lack of progressive disease. Complete response is a completely flat scar. A decrease of tumor thickness of more than 50% is partial response, while progressive disease is a tumor growth of more than 25%; the remaining responses are defined as stable disease.

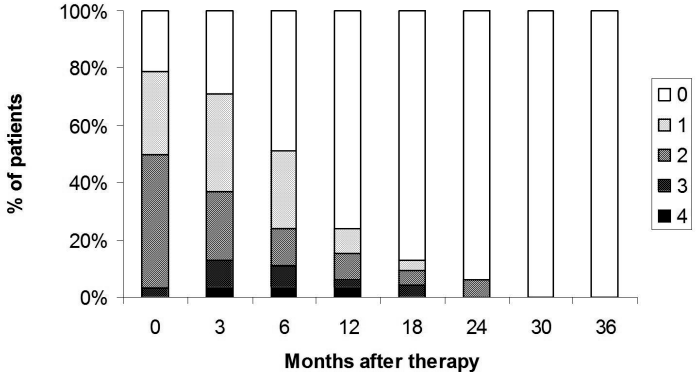
Visual acuity

Since it was expected that the course of best corrected visual acuity (BCVA) depended on the location of the tumor, patients were divided into posterior and anterior located tumors.

Retinal detachment

The amount of exudative retinal detachment was classified into 5 groups according to the EORTC scale (0 no detachment to 4 complete detachment) (Figure 3).

FIGURE 3 *Retinal detachment as a function of time of follow-up*
Four classes of detachment: 0= no subretinal fluid, 1= subtle fluid, 2= local fluid, 3 = detachment of half of the retina, 4= total ablatio. On the y axis the percentage of the total number of treated patients is presented.



Statistics

Since the distribution of the values was ordinal, the Wilcoxon Signed Rank Test was used to analyze the difference between the BCVA before and 12 and 24 months after therapy for all tumors as well as for anterior and posterior located tumors, separately.

Results

Dose in critical structures

Twenty-five percent of the volume of the ciliar body received a mean of 277 cGy per fraction, with a median of 167 cGy, while 11 patients received more than 250 cGy in at least 25% of the ciliar body.

The mean of the maximum doses in the optical nerve per fraction was 457 cGy (median: 351 cGy); 15 patients received more than the allowed 400 cGy per fraction in the optical nerve.

Tumor control

The local control up to now is 100% after a mean follow-up of 2 years, although it takes up to six months until a decrease in tumor thickness can be detected (Table 3). One year after fSRT 13 percent had partial response, while 87 percent had a stable disease, according to our definition. After 2 years the mean prominence was halved (Figure 4) and the percentage of patients having a partial response was increased to 36.

Three patients developed metastases, all located in the liver. In retrospect, 1 patient had a suspicious lesion in the liver at diagnosis. Two patients developed metastases 1 and 2 years after diagnosis, respectively.

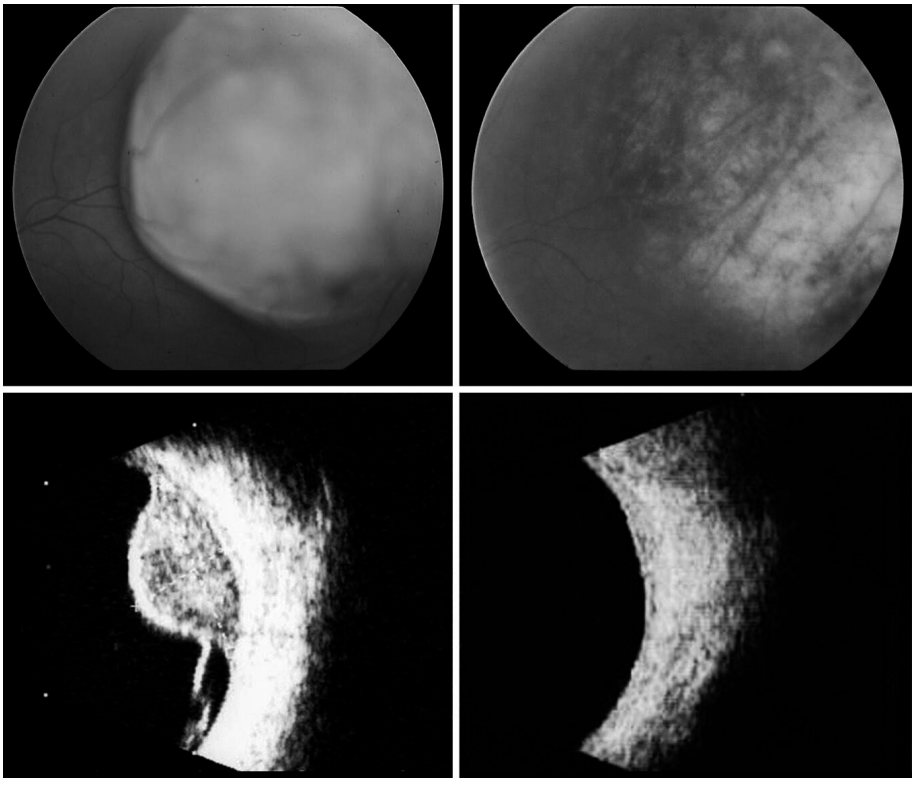
After a mean follow-up of 25 months the overall survival was 67%. Five patients died, of which 3 patients due to a melanoma related cause at 13, 26 and 30 months after therapy, respectively. One patient died due to metastasized ovarian cancer. The fifth patient died from peritonitis caused by a perforated gastric ulcer.

TABLE 3 *Tumor Regression (MM)*

Time of Follow-up	**Diameter**[1]			Prominence		
(number of patients)	Before	After	Effect	Before	After	Effect
3 months (38)	10.6	10.5	1%	6.4	6.2	3%
6 months (36)	10.4	10.0	4%	6.3	5.3	16%
12 months (32)	10.5	9.8	7%	6.2	4.6	26%
18 months (22)	10.4	9.4	10%	5.7	3.2	44%
24 months (15)	10.6	9.2	13%	5.3	2.7	47%

[1] Diameter: Mean of horizontal and vertical dimensions

FIGURE 4 *Example of decrease of prominence*
Female patient of 59 years, uveal melanoma in left eye; the prominence of 6.6-mm before treatment decreased to 0.6-mm 12 months after treatment; subretinal fluid vanished. Both ultrasonography scans were performed using 20 MHz (gain of 80, depth of 4-mm).

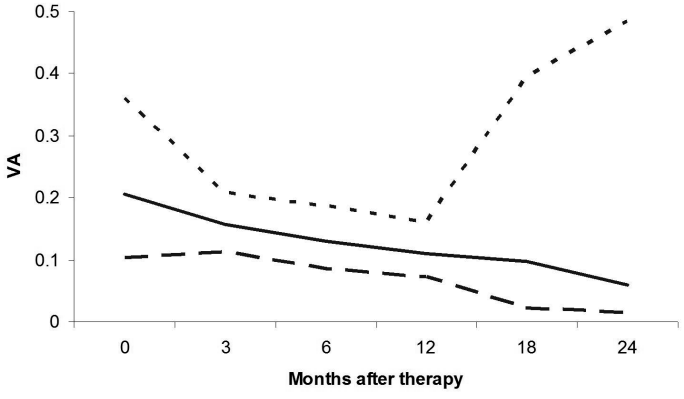


Toxicity

Visual acuity

The BCVA gradually declined from 0.21 at diagnosis to a mean acuity of 0.06 two years after therapy (Figure 5). A significant decline in VA was found in the posterior located tumors. For the anterior located tumors, no significant difference between the BCVA before and 2 years after therapy could be found. However, an initial decline of 42 percent at 3 months after therapy was seen.

FIGURE 5 *Best corrected visual acuity before and after therapy*
Best corrected visual acuity at diagnosis and after therapy for all tumors and for tumors located in the posterior (dashed line) or anterior (dotted line) part of the eye.



Retinal detachment

The retinal detachment before therapy was completely resolved two years after therapy (Figure 3). Three patients with a tumor in the posterior pole and subretinal leakage were treated with transpupillar thermotherapy to resolve the subretinal fluid; two patients were treated at 12 months and 1 patient at 22 months after therapy.

Side effects

The side effects are divided into subgroups as depicted in Table 4. The columns represent the symptoms after 3, 6, 9, 12 and 24 months of follow-up, respectively. During follow-up most patients did not experience any significant side effects.

Acute side effects

The most common symptoms after 3 months of follow-up were mild conjunctival symptoms, such as hyperemia, irritation, tears and chemosis, visual symptoms (light flashes, mononuclear diplopia, floaters and metamorphopsia), loss of hair or lashes and fatigue. One patient suffered from vitreous hemorrhage at diagnosis already. One patient underwent an enucleation 2 months after irradiation, because of total retinal detachment and suspicion of tumor growth. The pathologist however found massive inflammation; no vital tumor cells could be detected.

TABLE 4 *Clinical Symptoms*

Symptoms	Months after therapy *(number of patients)*				
	3 ***(38)***	**6** ***(36)***	**12** ***(32)***	**18** ***(22)***	**24** ***(15)***
No complaints	19	22	23	14	7
Conjunctival symptoms	10	3	1	1	0
Loss of lashes or hair	6	1	1	0	0
Visual symptoms	5	1	1	1	1
Fatigue	5	0	0	1	0
Pain	4	2	1	1	1
Dry eye	1	3	3	3	3
Cataract	1	0	1	0	0
Retinopathy	0	0	1	2	1
Optical neuropathy	0	0	2	2	1
Other[1]	1	3	4	2	1

[1] Branch retinal vein occlusion (1), subretinal bleeding (1), vitreous hemorrhage (2) and neovascular glaucoma (1)

Late side effects

One and 2 years after fSRT 64% and 47% of the patients remained free of serious late toxicity. The most serious adverse effects after 1 year of treatment were neovascular glaucoma (5%), retinopathy (5%), optical neuropathy (9%), dry eye (9%) and subretinal bleeding (5%). So far, no enucleations due to late side effects were required.

Discussion

Several eye sparing treatment options have been developed during the last couple of decades. The most suitable modality depends on both the size and the location of the tumor. Stereotactic radiation therapy has proven to be a good alternative for medium and large sized tumors [11-15, 19, 20]. Since a few years fSRT has been used with as important advantage the better sparing of normal tissues radiobiologically, by fractionating the dose and physically, by a 3-dimensional approach [21, 22].

Uveal melanomas are known to be relatively resistant to radiation [23, 24]. Van den Aardweg et al., analyzing the effects of split-dose irradiation on uveal melanoma cell lines, concluded that the radiosensitivity is dominated by the intrinsic factors, i.e. the α-component [25]. A total dose of 50 Gy, in 5 daily fractions of 10 Gy, should be sufficient to kill even the most radio-resistant tumor cells and yet, spare critical structures. However, a great variation in radiosensitivity between different cell lines was found indicating that this schedule is probably overkill for more sensitive cell lines. More research is necessary to determine specific morphologic and histological tumor markers in order to individualize dose fractionation schedules.

In this study, local control up to 2 years after therapy is excellent without progressive disease so far. These data are comparable to published results of other treatment modalities, such as brachytherapy [7, 20, 26-28], proton therapy [3, 4, 6-9, 29] and radiosurgery [11-15, 19, 20]. Although preliminary, these results demonstrate that fSRT is an effective treatment modality for medium and large sized uveal melanomas. Whether the extent of decrease in prominence of uveal melanoma is related to stable disease, partial or complete response is questionable.

The observed delayed tumor regression is also described by other authors [21, 30]. The reason for this delay can (partly) be explained by the development of edema as a reaction on radiation therapy as described in several articles about stereotactic radiation therapy for other tumor sites [31, 32].

Three out of 32 patients developed liver metastases 1 year after treatment. A longer follow-up however is needed to analyze the rate of metastases, since these tumors are known to metastasize rather late [33-35].

The BCVA two years after fSRT is disappointing. Several explanations for this result can be found. At first, half of the tumors were located in the posterior pole. From our analysis the BCVA of eyes with posterior located tumors was significantly worse when compared to the eyes with anterior located tumors, which had still a useful BCVA after therapy. Besides, most of the patients had declined vision at diagnosis already. Furthermore, the tumor size was considerable, with a mean diameter before therapy of 10.5 mm. Also, the mean distance of the tumor to the fovea was 3.6 mm. These properties are described as being risk factors for impaired VA in former publications of radiation therapy for uveal melanoma [3-5, 9, 28, 36]. A comparison with brachytherapy is difficult to make as the mean tumor size in this treatment group is often smaller (in particular the prominence) and the overall pre-treatment BCVA is better [7]. Nevertheless, given

the results, brachytherapy seems to be the preferred treatment for smaller posterior located melanoma. However, fSRT remains a useful treatment options for posterior located tumors too large for brachytherapy and for juxta papillary tumors. Even if there is no vision left, the bulbus as well as perception of light can still be preserved. The initial decline of BCVA in anterior located tumors of 25% after 3 months can probably be explained by vitreous hemorrhage that resolves during further follow-up.

The acute side effects were mild and mostly reversible. One eye was enucleated 2 months post fSRT on suspicion of tumor growth. The pathology however, described massive inflammation. No vital tumor cells were found. Consequently, this case is more likely to be a serious complication than tumor growth; reconstruction of the case showed a very high tumor dose. The late side effects so far turned out to be mild, although more serious effects such as retinopathy and optical neuropathy occurred after 1 year of follow-up, both in 2 patients. The conjunctival and visual symptoms seemed to resolve during further follow-up. However, a dry eye was more common. The other side effects enclosed a subretinal hemorrhage in 1 patient 1 year after treatment, a branch retinal vein occlusion in 1 patient after 2 years of follow-up and 1 vitreous hemorrhage 6 months after therapy. Neovascular glaucoma is often described in literature as a common late side effect [3-5, 7, 12, 14, 15, 19, 21, 37]. So far, neovascular glaucoma occurred just in 1 patient; the reason for this is perhaps the rather strict maximum dose criteria accepted for the anterior segment of the eye. Although preliminary, the incidence and degree of the side effects are promising as compared to the literature [3-7, 9, 10, 12, 14, 15, 19-21, 37, 38]. Alas the follow-up is too short and the number of patients is too small to draw firm conclusions.

Conclusion

In summary, fractionated stereotactic radiation therapy of uveal melanoma results in excellent local control with only mild side effects. Therefore, it seems to be an effective and safe treatment modality for uveal melanoma. However, the BCVA two years after therapy is declined, mainly because of the considerable tumor size and the location of tumor; half of the tumors were located in the posterior part of the eye. Finally, longer follow-up with a larger number of patients is needed for long-term local control, late toxicity and survival.

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Chapter 4

FRACTIONATED STEREOTACTIC RADIOTHERAPY FOR UVEAL MELANOMA
LATE CLINICAL RESULTS

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Abstract

Purpose

To determine local control, late toxicity and metastatic free survival (MFS) of patients treated with fractionated Stereotactic Radiation Therapy (fSRT) for uveal melanoma (UM).

Methods and Materials

Between 1999 and 2007, 102 UM patients were included in a prospective study of a single institution (median follow-up (FU) 32 months; median tumor thickness 6 mm); 5 fractions of 10 Gy were given. Primary endpoints were local tumor control and late toxicity (including visual outcome and eye preservation). Secondary endpoint was MFS.

Results

Local tumor control was achieved in 96% of the patients. Fifteen enucleations were performed, 2 to 85 months after radiation. Four eyes were enucleated because of local tumor progression. Nine patients developed grade 3 or 4 neovascular glaucoma (NVG), 19 developed severe retinopathy, 13 developed opticoneuropathy grade 3 or 4, 10 developed cataract grade 3 and 10 patients suffered from keratitis sicca. Best corrected visual acuity (BCVA) decreased from a mean of 0.26 at diagnosis to 0.16, 3 months after radiation and it gradually declined to 0.03, 4 years after therapy. The 5-year actuarial MFS was 75% (95% CIs: 62–84%).

Conclusions

fSRT is an effective treatment modality for uveal melanoma with a good local control. With that, fSRT is a serious eye sparing treatment modality. However, our FU is relatively short. Also, the number of secondary enucleations is substantial, mainly caused by NVG.

Introduction

Uveal melanoma (UM) is the most common primary eye cancer in adults [1]. Still, UM occurs infrequently, having an annual age adjusted incidence of 4 to 7 per million [1]. Generally, uveal melanomas arise from the choroid (72%); however, they may also appear in the ciliary body (23%) or iris (5%). Currently next to enucleation, patients can be offered several eye sparing treatment options. The preferred treatment is influenced by a number of patient and tumor related factors, such as general condition, age, size and location of the tumor, visual acuity of the contralateral eye and the presence of metastases at diagnosis. Beside radiotherapy, transscleral resection, transretinal resection and phototherapy are used for the primary treatment of uveal melanomas. It is beyond the scope of this paper however, to discuss these modalities.

Regarding radiotherapy, brachytherapy appears to be an effective treatment modality for UM [2-9]. For medium and large sized tumors, heavy particle radiation techniques (proton and helium ion beam) as well as stereotactic radiation therapy (SRT) are other eye sparing treatment options[10-14]. Single fraction SRT ("radiosurgery") for UM, has been introduced in 1987, with local control rates between 90 and 98 percent [15, 16]. The most important shortcoming of radiosurgery is the loss of radiobiological sparing of adjacent critical structures. Fractionated stereotactic radiotherapy (fSRT) reduces the effective dose in the surrounding tissues with a delivery of an equivalent effective dose to the tumor. 1999, a longitudinal cohort study has been initiated in our institute, in which patients with UM were treated with fSRT. Preliminary results demonstrated that fSRT is well tolerated and can be safely implemented in the treatment of UM with excellent short term local control and mild acute side effects [17, 18]. However, to determine the efficacy of fSRT, not only local control and survival at long-term, but also late toxicity is an issue to be studied in great detail. In this paper, the primary endpoints local tumor control and late toxicity, including visual outcome and eye preservation, as well as the secondary endpoint, metastastic free survival (MFS) of 102 UM patients are analyzed.

Methods and Materials

Study design

In 1999 a prospective single center clinical trial was initiated in order to study both the safety and efficacy of fSRT for UM. In this report the local control, late toxicity and survival up to 5 years follow-up (FU) were evaluated. Approval for this study was obtained from the Institutional Review Board at the Erasmus Medical Center. All patients signed an informed consent.

Patients of at least 18 years of age with a WHO performance status of 0 or 1 and with UM of choroid or ciliary body with a tumor thickness smaller than 12 mm, a diameter of smaller than 16 mm and no clinical evidence for metastatic disease were included. Between 1999 and 2007, 102 consecutive UM patients (58 male, 44 female) were included into the study. Both characteristics of patients and tumor data are presented in table 1.

Treatment planning

Patients were immobilized by means of a non-invasive relocatable Gill Thomas Cosman stereotactic frame (GTC frame™, Radionics, Burlington, USA) [19, 20], modified with the Rotterdam eye fixation system. A treatment plan was made using stereotactic arcs of 6 MV photons (XKnife RT™ 1.03, Radionics). A total dose of 50 Gy (5 fractions of 10 Gy) was delivered on 5 consecutive days. The Rotterdam eye fixation system and the treatment techniques per se, have been detailed in previous publications [17, 18].

Follow-up (FU)

Six weeks after irradiation, patients were examined, followed by a three monthly evaluation (including lab tests) during the first two years; after two years the examinations were every four months. The median FU was 32 months (2 to 92); one patient was lost to FU 48 months after initiation of therapy.

Analysis

Endpoints

Primary endpoints were local tumor control and late toxicity after 1 to 5 years, including visual outcome and eye preservation. The actuarial metastatic free survival (MFS), with 95% confidence intervals (CI), after 5 years was determined as the secondary endpoint.

TABLE 1 *General Data and Tumor Characteristics*

Characteristics	Median	(range)	N[a]
Age *(years)*	63	(28-83)	
Gender			
Male			58
Female			44
Follow-up *(months)*	32	(2-94)	
Size *(mm)*			
Diameter	11.9	(7.5-18.9)	
Tumor thickness	6.0	(2.2-11.1)	
TNM*			
T1a			18
T2a			45
T2b			2
T3a			33
T3b			2
T4a			1
T4b			1
Shape			
Dome			82
Mushroom			18
Diffuse			2
Laterality			
Right			38
Left			64
Location**			
Anterior [1]			55
Posterior [2]			41
Ciliary body			6

[a] Total number of patients is 102
* TNM staging of malignant melanoma of the uvea, 7th edition of AJCC
** Location of epicenter of the tumor
[1] Ora serrata and equator
[2] Post equator

Toxicity Scoring Criteria

The common terminology criteria for adverse events (CTCAE, version 3.0) was used, to evaluate toxicity [21-23], table 2. Retinal detachment was classified into 5 groups according to the EORTC scale (0 no detachment to 4 complete detachment). Visual acuity was determined: The best corrected visual acuity (BCVA) was converted into linear values in order to calculate the mean values of the group.

TABLE 2 *Toxicity*

	Grade [a]				
CTC	**1**	**2**	**3**	**4**	**Time at diagnosis** [b] ***(months)***
cataract	8	5	10	-	12 (3-42)
dry eye	8	8	2	-	6 (3-24)
glaucoma *	2	2	3	6	30 (12-60)
keratitis	3	4	3	0	6 (3-12)
Optic disc edema	0	2	9	4	18 (12-24)
retinopathy	10	11	13	6	24 (12-72)
uveïtis	0	1	1	0	6
vitreous haemorrhage	2	4	4	-	15 (3-48)

[a] Total number of patients
[b] Median (range)
* All caused by neovascular glaucoma

Dose calculation

For all patients minimum (D_5) , median (D_{50}) and maximum (D_{95}) doses of both PTV and critical structures were calculated. The dose given in at least 25 percent of the ciliary body (lens included) (D_{25}) was also computed, since this was a planning constraint.

Statistics

Logistic regression analyses were performed to analyze the relationship between the risk on toxicity versus possible risk factors (such as dose and tumor size and location). Tests with a *p* value of less than 0.05 were considered to be significant.

MFS was calculated using the actuarial method. We calculated time to first detection of metastases.

Results

Local tumor control

In general, tumor thickness started to decrease 6 months after initiation of radiation therapy. Of the 102 tumors, 6 remained stable in thickness and underwent within a time frame of 10 to 27 months transpupillar thermotherapy. These tumors were located equatorial (2) or post-equatorial (4); none of the ciliary body tumors failed. There was no correlation with diameter or tumor thickness and local failure ($p=0.3$). Eventually, out of these 6 patients, 4 had to be enucleated after a median FU of 40 months (14-85 months) due to tumor progression.

Toxicity

Ten patients developed cataract grade 3; all of these underwent a lens extraction, followed by an implantation of an intraocular lens. Patients that received a higher dose into the lens and ciliary body appeared to have a higher probability of developing a cataract grade 3. The logistic regression analysis outcome for developing a cataract grade 3 by radiation therapy with minimum, median and maximum doses appears to be significant (that is $p=0.01$, $p= 0.003$ and $p=0.003$, respectively). A median dose of 5 Gy/fraction in the lens and ciliary body caused a cataract in 50 percent of the cases (TD50, see also figure 1a).

In 19 patients grade 3 and/or 4 retinopathy occurred. No significant influence was found of tumor thickness, diameter, maximum dose and the distance to the fovea. Thirteen patients developed grade 3 or 4 opticoneuropathy. The received median dose ($p=0.02$) and maximum dose ($p<0.001$) in the optical nerve and the distance between the PTV and the optical nerve ($p=0.01$) were statistically significant predicting factors for opticoneuropathy (figure 1b). A maximum accepted dose of 4 Gy/fraction in the optical nerve corresponded with a 10% probability of severe opticoneuropathy; the TD50 was 9.6 Gy/fraction.

Before treatment, retinal detachment (RD) was present in 57 patients, varying from grade 1 to grade 3. In 11 cases, RD aggravated directly after radiation therapy. Eight patients were treated for RD with Triamcinolone, 4 of which underwent a vitrectomy in the course of FU. Two out of 5 patients, who developed RD grade 4, had to be enucleated (1 because of secondary endophthalmitis after vitrectomy). Eventually, RD resolved in the rest of patients within 2 years. Larger melanomas (in thickness and

diameter) showed to have a higher probability of a grade 3 and 4 RD ($p<0.001$ and $p=0.001$, respectively). A tumor thickness of 9.6 mm corresponds with a 50% probability on grade 3 or 4 RD. Also, grade 2 or 3 RD before treatment appeared to be a prognostic predicting factor for the development of grade 3 and 4 RD ($p<0.001$).

Nine patients developed grade 3 and 4 neovascular glaucoma (NVG), and 8 of them had to be enucleated. Tumor thickness ($p=0.02$) and the appearance of grade 3 retinopathy ($p=0.003$) were predicting factors. The minimum, median and maximum doses received in the ciliary body were not significantly different compared to patients without glaucoma.

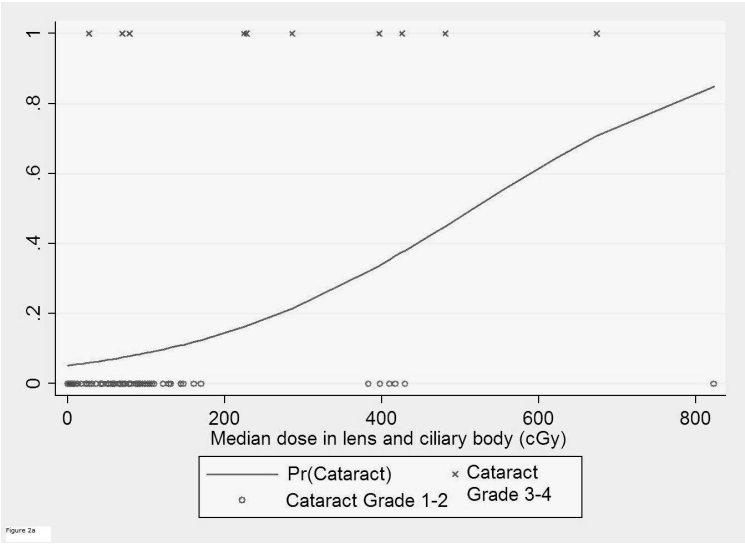
Ten patients developed dry eye syndrome (DES) grade 2 and 3. One patients had temporarily acute symptoms of DES. A clear relationship between the appearance of DES and dose to the lacrimal gland was found; this is reported in detail (Muller *et al 2009)* [18].

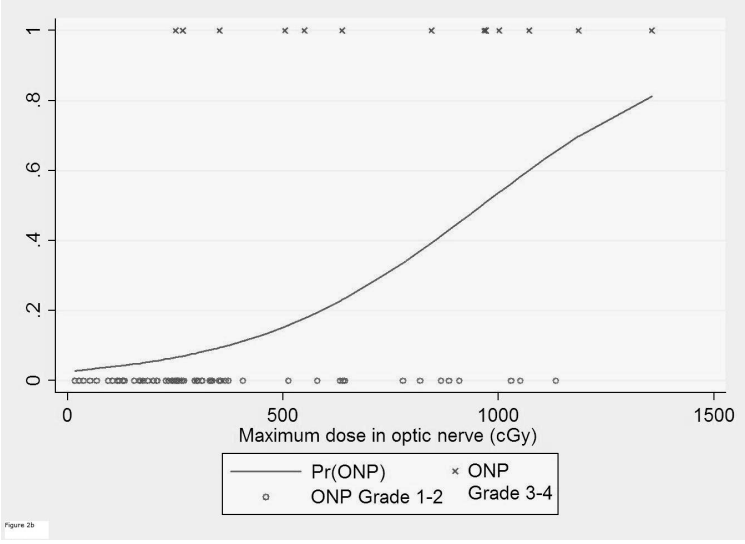
Visual acuity

Directly after radiation, the best corrected visual acuity (BCVA) decreased from a mean of 0.26 at diagnosis to 0.16 after 3 months of FU, after which it gradually declined to 0.03, 4 years after therapy. Particularly in posteriorly located tumors, the BCVA decreased to < 0.1. Anterior located tumors showed a stable BCVA with a mean of 0.16 after 4 years. Tumor location was correlated with both preoperative vision ($p=0.048$) and BCVA after 18 months of FU ($p=0.02$; even when corrected for preoperative vision). Also, a higher maximum dose to the optical nerve corresponded to a lower visual outcome ($p< 0.05$). Neither tumor thickness nor diameter correlated with BCVA. A low pre-irradiation BCVA score did show a statistically significant correlation with low visual outcomes after treatment.

FIGURE 1 *Graphs of logistic regression analysis; toxicity versus dose*
The y-axis represents the appearance of cataract grade 3 (figure 1a) or optic neuropathy grade 3 or 4(figure 1b): 0 is no toxicity grade 3 or 4, 1 is toxicity grade 3 or 4; on the x-axis the dose delivered in the lens and ciliary body (figure 1a) or optical nerve (figure 1b) is pointed out; each cross and circle represents a single patient; the drawn line depicts the chance on toxicity versus the dose.

a. Cataract versus median dose in lens and ciliary body (cGy/fraction)
b. Optic neuropathy (ONP) versus maximum dose in optic nerve (cGy/fraction)





Eye preservation

Because of various causes as listed in table 3, 15 patients were enucleated 2 to 85 months after radiation. One patient developed secondary endophthalmitis after vitrectomy. At the onset of the study, one patient was enucleated 2 months after fSRT on suspicion of tumor growth. The pathology however, described massive inflammation. Tumor thickness was not a significant prognostic factor for enucleation (p=0.15).

Metastatic free survival (MFS)

The 5-year actuarial MFS was 75% (95%CI: 62-84%). Fourteen patients developed distant metastases. In all cases the liver was affected, but also metastatic deposits were found in the lung (1 case), the peritoneum (1 case), a lymph node near the hepatojejunal ligament (1 case) and the skin (1 case). In the univariate analysis, no significant prognostic factors could be established for distant metastases, although a trend was seen for diameter (p=0.080) and tumor thickness (p=0.15).

TABLE 3 *Causes of Enucleation*

Description	**Frequency** [a]	**Time of Follow-up** [b] ***(months)***
Progression	4	40 (14-85) [b]
Toxicity	9	
Neovascular glaucoma	8	33 (16-55)[b]
Retinal detachment	1	14
Endophthalmitis after vitrectomy	1	9
Massive inflammation mistaken as progression	1	2

[a] Total number of patients
[b] Median (range)

Discussion

New eye sparing treatment modalities for UM have emerged and reported in the last decades [4, 15, 18, 24-28]. One of these new modalities is the use of fSRT. This paper reports on the results of fractionated SRT of a single institution with patients treated between 1999 and 2007. In our study we tried to describe not only the local tumor control and late toxicity, but also relate it to radiation dose and tumor characteristics.

Local tumor control

We found an overall local tumor control rate of 96%. Because of stable disease, transpupillar thermotherapy (TTT) was applied in 6 patients; eventually, 4 failures after fSRT and TTT had to be enucleated. The median time to progression was 3 years. Dieckman et al reported on a series of 90 patients, treated with a similar radiation scheme; a local control rate of 98 percent was observed [29]. Other reports on the use of SRT reported control rates of 91 to 97 percent [15, 16, 18, 28, 31, 32]. These data are also in agreement with other radiation modalities in literature [10, 12, 16, 29, 32-34]. The role of TTT in UM however, is debatable [4].

Toxicity

The BCVA was disappointing, especially in posteriorly located tumors. Visual outcome is variably reported in the literature [9, 35-37]. The visual acuity before treatment was clearly correlated with the visual outcome after treatment, which is in agreement with literature [15, 16, 37]. Also, the occurrence of retinopathy and or opticoneuropathy have negative impact on the visual outcome. In our population, 18% developed grade 3 or 4 retinopathy. In literature, retinopathy was reported in 10 to 81% of the cases [5, 29, 32, 33]. It is well known that the occurrence of (severe) radiation retinopathy is dose dependent: both high total doses (>25 Gy) as well as a high dose per fraction (>2 Gy) are well accepted known risk factors [38, 39]. However, in contrast to the literature, in this study no other significant factors were found for retinopathy [39].

Thirteen patients (13%) developed opticoneuropathy grade 3 or 4, which is in accordance with the reported 20% after fSRT in literature [29]. Other treatment modalities show opticoneuropathy rates of 8 – 46 % (BT) and 8 – 23% (proton therapy) [5, 33, 41, 43,44]. Predicting factors for optic neuropathy were tumor location and dose received in the optic nerve. The maximum dose we accepted in the optical nerve, i.e. 4Gy/fraction, corresponded with a 10% chance on developing opticoneuropathy.

Similar to the data published for brachytherapy [40, 41] and for periocular located tumors [42], the occurrence of grade 3 cataract in (10% of) our patients was clearly dose dependent.

Neovascular glaucoma (NVG) appeared to be the most serious complication of fSRT. Although grade 3 or 4 NVG occurred only in 9 patients yet (table 2), out of these 9, eight had to be enucleated. This number of NVG compares favorably with published NVG rates of 9 – 60% [29, 32, 33, 36, 41, 44]. However, our FU is relatively short. Contrary to

what we expected, the tumors of these 9 patients were not located anteriorly, nor did they receive a substantial higher dose to the ciliary body [43]. Tumor thickness and the occurrence of radiation retinopathy grade 3 turned out to be predicting factors for NVG, which is also reported in literature [41, 44]. Our hypothesis is that the physical reaction on ischemic retinopathy, such as vascular proliferation, might also affect the vessels in the ciliary body, with NVG as a result. Hopefully, in near future, better understanding and treatment of NVG with new techniques, such as iridocyclectomy, will decrease the number of secondary enucleations [41].
The use of univariate analyses may not be accurate in view of the multifactorial etiology of most toxicities. However, due to the small numbers of our study it was not possible to run multivariate analyses.

Metastatic free survival(MFS)
In this study the 5-year actuarial MFS was 75%. This is comparable with the survival outcome of proton beam therapy for similar sized tumors [10, 36]. According to literature, in case of a local recurrence, the metastases rate increases [14, 45-49]. However, in this study only 4 patients developed local recurrence and 1 of these developed metastases. These numbers are in fact too small to draw any meaningful conclusions. Given the literature, tumor size appears to be an important predictor for both overall- and metastatic free survival [50]. Although there was a trend for larger tumors to develop more metastases, this was not significant. However, numbers of patients are small and FU time might not be sufficient, since uveal melanomas metastasize relatively late. In concordance with the literature, our patients survived after developing metastases a median of 9 months [4, 51-57].

Limitations and challenges:
In our study, the number of patients is relatively small and median FU might be too short. Keeping this in mind we are apprehensive in drawing conclusions out of the results of our series. From the onset of our study we realized that a long FU would be preferable in UM patients. Therefore, the FU of our patient cohort is still ongoing and we will re-evaluate our results after a longer period of FU. Also, due to the rare incidence of uveal melanomas, it was not possible to start a randomized study in which fSRT could be compared with other treatment modalities, such as brachytherapy, proton therapy and enucleation. It is of interest however, not only to compare our data

set to literature, but to compare our data with equal tumor and patient characteristics treated with other eye sparing modalities and enucleation. Currently, our data are being compared with the patients treated with brachytherapy at the LUMC (Leiden) and will be published soon. Another difficulty in inter-study comparison of results is the existence of different toxicity grading systems. Unfortunately, since they all have their specific (dis-)advantages, there is no clear cut solution for this problem. Finally, from the onset of our study, quality of life questionnaires were given to all UM patients before treatment (fSRT or enucleation) and during FU. In near future, we will evaluate the quality of life of patients treated with fSRT versus enucleation; this will be combined with cost-benefit analyses.

Conclusion

In conclusion, fSRT turned out to be an effective treatment modality for uveal melanoma, with a good local control. With that, fSRT is a serious eye sparing treatment modality comparable to other external beam techniques. However, our follow-up up to this point is short and the number of patients relatively small. Also, the number of secondary enucleations is substantial, mainly caused by NVG. Furthermore, the morbidity is influenced by tumor size and location. Treatment preference should be based on tumor characteristics and patient's preferences.

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Chapter 5

LACRIMAL GLAND RADIOSENSITIVITY IN UVEAL MELANOMA PATIENTS

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Abstract

Purpose

To find a dose volume effect for (inhomogeneous) irradiated lacrimal glands.

Methods and Materials

Between 1999 and 2006, 72 patients (42 male, 30 female) were treated with fractionated stereotactic radiation therapy in a prospective, nonrandomized clinical trial (median FU of 32 months). A total dose of 50 Gy was given on 5 consecutive days. The mean of all Schirmer test results obtained six and more months after treatment, was correlated with the radiation dose delivered to the lacrimal gland; also, the appearance of dry eye syndrome (DES) was related to the lacrimal gland dose distribution.

Results

Seventeen patients developed a late Schirmer value below 10 mm; 9 patients developed DES. There was a statistically significant relationship between the received median dose in the lacrimal gland versus reduced tear production ($p=0.000$) and the appearance of DES ($p=0.003$), respectively. A median dose of 7 Gy/fraction to the lacrimal gland caused a 50 percent chance of low Schirmer results; a median dose of 10 Gy a 50 percent probability of DES.

Conclusions

There is a clear dose volume relationship of irradiated lacrimal glands with regard to reduced tear production and the appearance of DES.

Introduction

The lacrimal gland is the main tear secretor of the eye and contributes in particular to the production of the middle aqueous layer of a tear film [1]. This aqueous layer plays an important role in the lubrication of the eye: It supplies oxygen to the corneal epithelium, prevents infections, abolishes irregularities of the cornea and removes debris from the conjunctiva and cornea [2]. If the lacrimal gland is affected by radiation, a dry eye syndrome (DES) can occur [3-7]. Irradiation of the lacrimal gland can result, after a latent period of approximately 6 months, in chronic inflammation and eventually in fibrosis and atrophy. [3, 6, 7, 13]. Finally, at a dose level of ≥ 40 Gy when applied to the whole organ, that is the orbit, a clear dose effect relationship has been established [3-7, 12, 14-25]. Some of the new 3-D computer-planning systems enable one to apply very conformal dose distributions. Therewith, in case of orbital tumors, the critical surrounding normal tissues such as the lacrimal gland can be (partly) spared.
The purpose of this study is to investigate whether a dose volume relationship exists and consequently, a dose constraint can be established for the lacrimal gland.

Methods and Materials

Patient characteristics and tumor data
Between 1999 and 2006, 72 uveal melanoma patients (42 male, 30 female) were treated with fractionated stereotactic radiation therapy (fSRT), consecutively in a prospective one-center clinical trial in order to study the local tumor control, side effects and melanoma-related death. All patients signed an informed consent for irradiation in this trial.
During the clinical trial nine patients developed DES. Because of the development of DES in few patients, Schirmer tests (ColorBar™, Eagle Vision, US) were included in the routine ophthalmologic investigations, one year after the initiation of the clinical trial. For our analysis we compared the patients with DES versus no DES and also the patients with low Schirmer results versus normal Schirmer results to the dose delivered in the lacrimal gland. The patient demographics are summarized Table 1.

TABLE 1 *General Data and Tumor Characteristics*

	Total (n=72)			**No DES (n=63)**			**DES (n=9)**			
	Mean	**(range)**	**N**	**Mean**	**(range)**	**N**	**Mean**	**(range)**	**N**	***p* value**
Age *(years)*	62	(28-82)		62	(28-81)		62	(38-82)		0.96
Gender										0.15
Male			42			39			3	
Female			30			24			6	
Size *(mm)*										
Diameter										
Horizontal	11.5	(7.5-18.9)		11.5	(7.5-18.9)		11.9	(8.4-16.0)		0.53
Vertical	10.1	(6.5-14.9)		9.9	(6.5-14.9)		10.9	(6.5-14.6)		0.60
Prominence	6.1	(2.2-10.9)		6.1	(2.2-10.9)		6.5	(3.4-8.2)		0.24
Schirmer *(mm)*										
pre-treatment	21	(5-35)		21	(5-35)		25	(10-35)		0.60
acute	21	(5-35)		19	(5-35)		21	(10-28)		0.99
late	18	(3-35)		22	(3-35)		6.6	(5-9)		0.00
<10 mm			17			8			9	0.00
Dose in lacrimal gland *(cGy/fraction)*	326	(7-1005)		284	(7-1005)		612	(201-962)		0.00
Follow-up *(months)*	32	(6-74)		31	(6-74)		34	(13-59)		0.66

Radiation

A total dose of 50 Gy in 5 fractions was delivered on 5 consecutive days. The dose was prescribed to the 80% isodose surface, encompassing the planning target volume (PTV). There was no dose prescription for the lacrimal gland. More details about the treatment are described in former articles [8, 9].

Follow-up

Patients were examined at 3, 6 and 12 weeks after completion of irradiation, followed by a three-monthly evaluation during the first year; thereafter the examinations were every four months. The median follow-up was 32 months (6 - 74). No patients were lost to follow-up. All patients were asked for their symptoms and keratitis was examined using a slit lamp. In case of keratitis or dry eye complaints, fluorescein staining was used to asses the tear film break-up time and punctuate keratitis. Of all patients Schirmer

tests (ColorBar™, Eagle Vision, US) were performed on both the affected and the contralateral eye before treatment (51 patients) and at each follow-up appointment. A Schirmer strip was inserted into the temporolateral side of the lower fornix without anesthesia and was measured after 5 minutes. A mean of the values of 3, 6 and 12 weeks and 3 months was taken as the acute Schirmer value; the mean of the results of 6 months and later was considered to be the late Schirmer value.

Analysis

Definitions

Toxicity scores

The common terminology criteria for adverse events (CTCAE, version 3.0) were used to describe both the frequency and severity of DES and keratitis [11]. Also, RTOG (Radiation Toxicity Oncology Group) acute radiation morbidity scoring criteria and the RTOG/EORTC late radiation morbidity scoring scheme were used to grade radiation-keratitis from no (grade 0) to severe (grade 3) keratitis (http://www.rtog.org/members/toxicity/late.html)[10].

Schirmer

The mean of the measurements of the Schirmer was calculated for both acute and late values as described above. A mean result of 10 millimeters (mm) or less after 5 minutes was considered as reduced. Because it took 6 months for the Schirmer results to drop, only the late values were used for the analysis (figure 1).

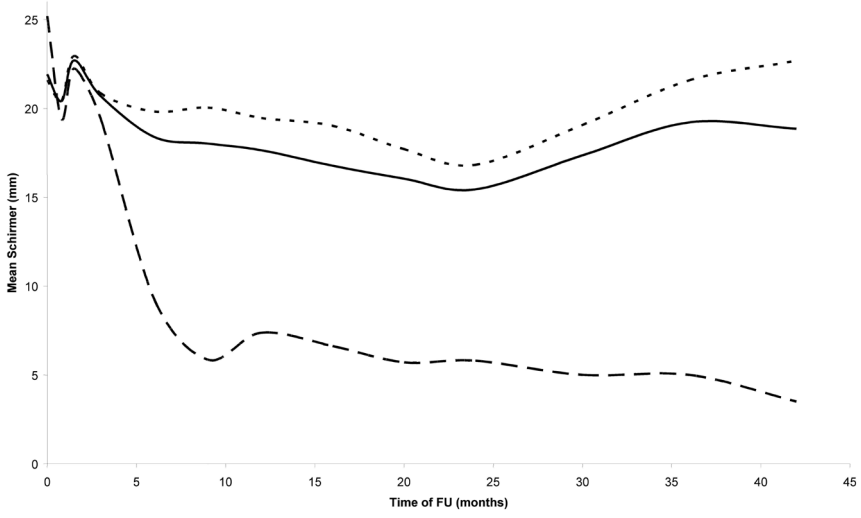
Dose calculation

Of all patients the maximum dose (D_5), the median dose (D_{50}) and the minimum dose (D_{95}) delivered in the lacrimal gland, respectively, were calculated. Also, the mean radiation dose to the lacrimal gland of each patient was determined.

Statistics

To analyze the relationship between the risk on DES and low Schirmer results versus dose delivered in the lacrimal gland , logistic regression analyses were performed. A *P* value of less than 0.05 was considered to be significant.

FIGURE 1 *Course of Schirmer during time of FU*
Mean Schirmer test results as a function of time of FU; The black line represents the mean Schirmer test results of the entire patient population over time; the striped and dotted lines represent the course of the Schirmer test results during follow-up of patients with DES and no DES, respectively.



Results

Schirmer

Seventeen patients had late Schirmer values below 10 mm, of which 3 had Schirmer results of less then 10 mm before treatment. Seven patients did not undergo a pre-treatment Schirmer test. The remainder developed decreased Schirmer test results after 6 to 9 months of FU. The change in the Schirmer test result over time is shown in Figure 1.

Eight patients with low late Schirmer test results had no complaints of dry eye.

Symptoms

After a minimum of 6 months of FU, 9 patients developed complaints due to DES, which arose 3 to 6 months after therapy (with only one exception of 24 months; Table 2).

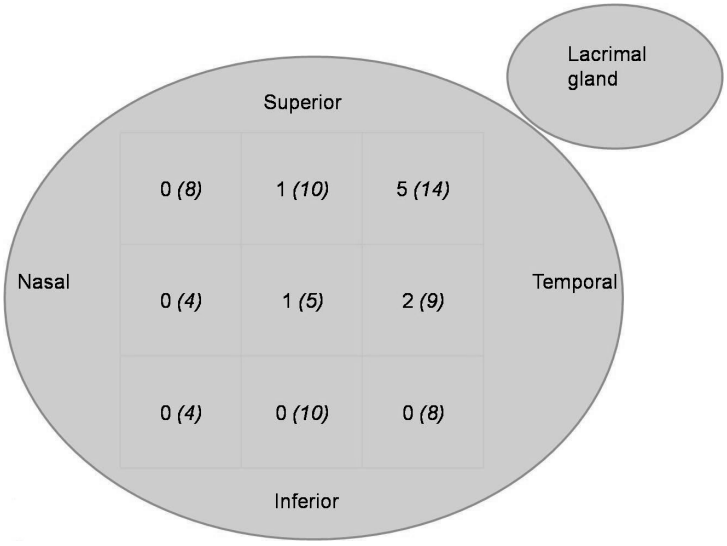
All patients with complaints of dry eye had low late Schirmer test results.

The location of the tumors with regard to the lacrimal glands for patients with DES and no DES is illustrated in Figure 2.

TABLE 2 *Side effects*

	Grade *(Number of patients)*				
	0	**1**	**2**	**3**	**4**
RTOG					
Acute	61	7	3	0	
Late	64	2	3	3	
CTC					
Dry eye	62	3	3	4	
Keratitis	61	6	3	2	0

FIGURE 2 *Position of the tumors with regard to the lacrimal gland*
Schematic view of location of the tumors with regard to the eye; the positions are divided into 9 subgroups: Nasal, central and temporal located tumors and cranial, central and caudal located tumors. The numbers represented are the absolute numbers of patients with DES within that relative compartment (between brackets: total number of patients within relative compartment).



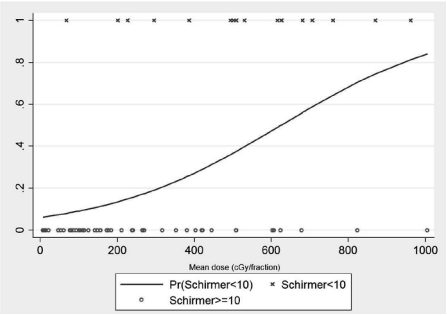
Endpoints

Schirmer versus dose in lacrimal gland

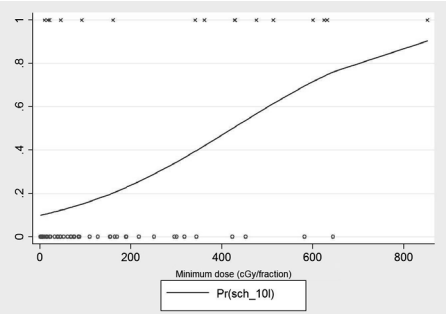
There was a statistically significant relationship between a late Schirmer test result of less than 10 mm versus the mean dose (p=0.001) and the D_5 (p=0.000), D_{50} (p=0.000) and D_{95} (p=0.001) delivered in the lacrimal gland, respectively.

A mean dose of the lacrimal gland of 6 Gy/fraction and a median dose of 7 G/fraction caused a reduced tear production in 50 percent of the cases (i.e. TD50; Figure 3).

FIGURE 3 *Graphs of logistic regression analyses of Schirmer test results versus dose in lacrimal gland*
The y-axis represents the Schirmer test result: 0 for Schirmer >= 10, 1 for Schirmer < 10; on the x-axis the dose delivered in the lacrimal gland is pointed out; each cross and circle represents a patient; the drawn line depicts the chance on a Schirmer result of <=10 versus the dose.
a. Schirmer test results versus median dose in lacrimal gland (cGy).
b. Schirmer test results versus minimum dose (D95) in lacrimal gland (cGy).

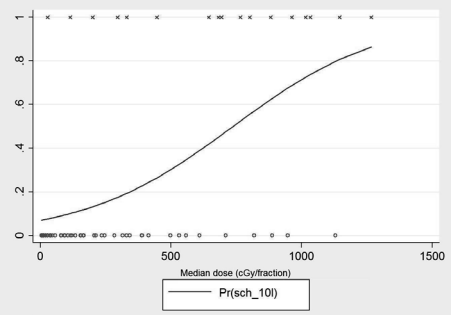


a.

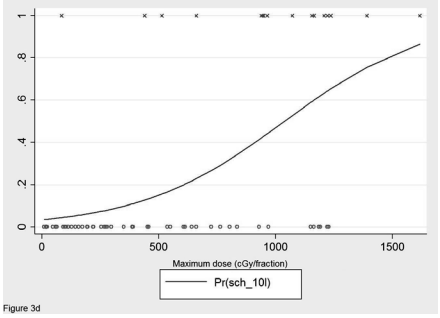


b.

c. Schirmer test results versus mean dose (D50) in lacrimal gland (cGy).
d. Schirmer test results versus maximum dose (D95) in lacrimal gland (cGy).



c.



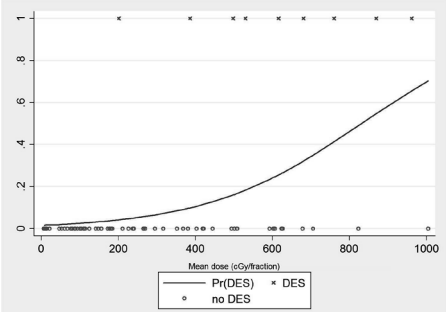
d.

DES versus dose in lacrimal gland

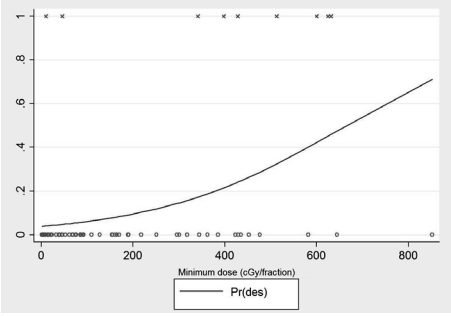
Patients with DES received a significantly higher mean (p=0.003), minimum (p=0.005), median (p=0.003) and maximum (=0.003) dose in the lacrimal gland compared to patients with no DES.

According to Figure 4, a mean dose of 8 Gy/fraction and a median dose of 10 Gy/fraction was associated with a 50% probability of DES (TD50).

FIGURE 4 *Graphs of logistic regression analyses of DES versus dose in lacrimal gland. The y-axis represents the appearance of DES: 0 is no DES, 1 is DES; on the x-axis the dose in the lacrimal gland is pointed out; each cross and circle represents a patient; the drawn line depicts the chance on DES versus the dose in the lacrimal gland.*
a. DES versus median dose in lacrimal gland (cGy).
b. DES versus minimum dose (D95) in lacrimal gland (cGy).

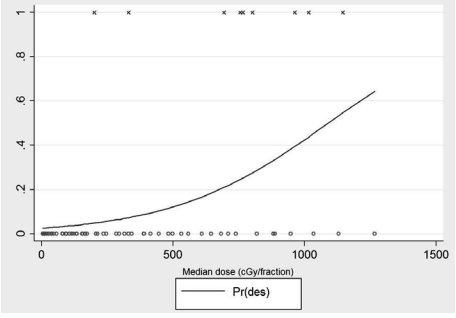


a.

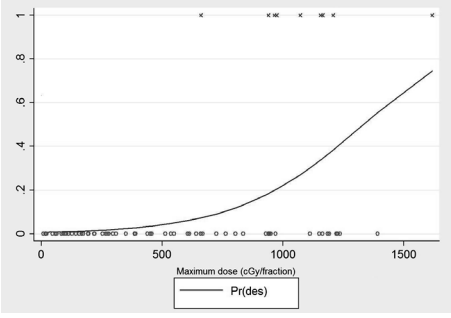


b.

c. DES versus mean dose (D50) in lacrimal gland (cGy).
d. DES versus maximum dose (D95) in lacrimal gland (cGy).



c.



d.

Discussion

The main lacrimal gland is the exocrine orbital gland and plays a dominant role in the aqueous tear secretory system [1]. Dysfunction of this gland results in DES, with serious complaints such as uncomfortable itchy eyes, foreign body sensation and photophobia [2]. Orbital irradiation can result in decreased tear production due to the integral dose received by the lacrimal gland [3-7]. With regard to DES, a clear dose effect relationship has been reported in the literature for whole orbit irradiation [3-7, 12, 14-25]. However, current radiation techniques, such as stereotactic irradiation and intensity modulated radiation therapy (IMRT), can tailor the dose more precisely to the planning target volume (PTV), therewith sparing the lacrimal gland. Given the fact that many of the departments of radiation oncology now routinely use 3D- treatment planning systems (3D-TPS) we found it to be of interest to study the dose effect relationship for the lacrimal gland in more detail.

The aim of the current research was to obtain the normal tissue complication probability (NTCP) for the non-uniformly irradiated lacrimal gland. Regarding the NTCP, the model of Lymann-Kutcher [26-32] is frequently cited. The non-universal outcome, however, reflects to a certain extend that this model is based on a number of assumptions. Moreover, in order to fit our data into the model, our irradiation schedule of 5 fractions of 10 Gy had to be "translated" into a 2 Gy/fraction model, which again complicates the applicability of the Lymann-Kutcher model [31, 33]. In this paper, for simplicity reasons it was elected to calculate a median threshold dose.

Figure 4 represents the dose effect relationship for DES in case of irradiation of the lacrimal gland; a median threshold dose of 10 Gy/fraction can be observed (TD50). It is of interest that even at a relatively low dose, a number of patients apparently complain of dry eye syndrome. However, if the tumors were located in the nasal and/or inferior part of the globe, no DES was found (figure 2).

Besides the dose-related dry eye syndrome, it is important to realize that according to literature some systemic diseases and drugs, such as beta-blockers and diuretics, are also associated with DES. For the study population of this paper, affected patients were screened for relevant systemic co-morbidity and medication [36, 37, 42-44]. That is, of the 9 patients 4 were found with hypertension [34-37], 2 with hypercholesterolemia and 1 with diabetes [37-41]. However, in the affected patients with systemic disease and/ or drug use, Schirmer test results before treatment and of the contralateral eye were excellent.

Therefore, there was no indication for possible blending of side effects and thus, DES seems to be related to dose only.

The diagnosis of dry eye, is hampered by the lack of sufficient discriminatory diagnostic tests [45, 46], especially in mild cases. Although the Schirmer test is one of the most valuable tests to measure the (aqueous) tear production, the uncertainty of the cut-off value and its (daily) fluctuations are important limitations [41, 45, 47, 48]. We elected a cut-off point of 10 mm to eliminate false negative results. A mean value was used to diminish the variation.

In this study, all patients with DES had low Schirmer results. Moreover, low Schirmer values were associated with significantly higher doses to the lacrimal gland (figure 3). However, half of the patients (8) with altered low late Schirmer results had no complaints of DES. It is well known that DES is multifactorial; even without radiation damage to the lacrimal gland, patients can still develop DES symptoms e.g. because of an unstable tear film being the result of radiation damage to Goblet cells in the conjunctiva and the small glands in the eyelid, structures supplying the fatty layer in the tear film [1, 2].

Other possible disturbing factors for the outcome of the Schirmer test are age [37, 41, 42, 49] (although this is not universal [50-52]) and female gender [36, 37, 41, 42, 50, 52, 53]. Both factors were equally distributed between the DES- and no DES groups.

Obviously, our study has its shortcomings. First, we started with Schirmer test one year after the initiation of the SRT trial of uveal melanoma, with as most important raison the incidence of DES and KS in a few patients. As a clear consequence, the pretreatment Schirmer results of these patients are lacking. Fortunately, we could draw on the values of the contralateral eyes.

Furthermore, although a respectable group of treated patients, the number of patients with DES is rather small. To draw conclusions out of such a small group contains a certain risk. On the contrary, the differences of both groups (with and without DES) were considerable and despite the small number of DES patients a clear relationship between the appearance of DES and the mean dose received in the lacrimal gland could be established. Moreover, since we started to spare the lacrimal glands, we were able to reduce the number of DES in nearby located tumors considerably.

Conclusion

DES due to irradiation occurs rarely in fSRT of uveal melanoma. When novel irradiation (sparing) techniques are used (as is the case in fSRT), sparing of the lacrimal gland is feasible. In our study, a clear dose/volume relationship with regard to the appearance of DES and tear production was found.
However, for a dry eye to be associated with significant complaints (DES) one needs to appreciate that the DES is a multifactorial process. This is exemplified by the fact that in our study population half of the patients with a low tear production do not complain of DES.

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Chapter 6

BRACHYTHERAPY VERSUS STEREOTACTIC RADIOTHERAPY

WHAT IS BEST IN CHOROIDEAL MELANOMAS?

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Abstract

Purpose

To compare survival and secondary enucleation rate of patients with choroidal melanoma treated with Ruthenium-106 brachytherapy (Ru-106) versus stereotactic radiotherapy (SRT).

Methods and materials

We included patients treated for medium size choroidal melanoma with either Ru-106 or SRT in the Leiden University Medical Center (LUMC) and the Erasmus Medical Center (EMC) from January 2000 till December 2007 with a tumor prominence between 2 and 8 mm. In order to obtain comparability between patients treated with Ru-106 and patients treated with SRT, all records were abstracted uniformly to make it impossible to identify patient and treatment center. Ophthalmologists from LUMC and EMC assessed these anonymous charts to indicate their treatment preference. Patients were assumed to be prognostically interchangeable when a different preference was expressed (one physician selecting Ru-106, the other SRT). The original treatment of these patients was used for a retrospective comparison of outcomes. Primary endpoints were overall survival (OS), metastatic-free survival (MFS) and secondary enucleation.

Results

228 patients treated with Ru-106 and 39 patients treated with SRT were selected according to this analysis based on prognostic interchangeability. 5-year OS of the patients treated with Ru-106 was 76,6% and 77.4% for the SRT group (p=0.37). 5-year MFS was 80.3% and 82.3%, respectively (p=0.59). 9.6% of the Ru-106 group and 15.4% of the SRT group underwent enucleation (p=0.36), in the Ru-106 group the mainly due to local recurrence (55%); in the SRT group mainly due to toxicity (67%).

Conclusion

No significant differences were found in survival and secondary enucleations for patients treated with Ru-106 compared with SRT.

Introduction

Choroidal melanomas are treated differently depending on size, prominence and availability of treatment modalities. Various eye sparing treatment modalities have been developed during the last decades. For small and medium sized choroidal melanomas, plaque brachytherapy (using Ruthenium-106 or Iodine-125) has proven to be effective in avoiding enucleation [1-7]. The use of brachytherapy is however limited to a maximum tumor prominence. For (medium to) large sized melanomas external beam radiation techniques have been developed [8-21]. At Leiden University Medical Center (LUMC) choroidal melanomas with a maximum prominence of 8 mm are treated with brachytherapy using a Ruthenium-106 applicator (Ru-106) [22-24]. In 1999, stereotactic radiotherapy (SRT) was introduced at Erasmus University Medical Center for treatment of melanomas up to a prominence of 12 mm [19,25]. A substantial proportion of the medium sized choroidal melanomas could thus be treated with either of both radiation methods. The main goal of our study was to determine the differences in clinical and survival outcomes after Ru-106 and SRT, respectively, for choroidal melanomas of comparable size.

Methods and Materials

Patient selection

We analyzed all choroidal melanomas with a prominence of 2 to 8 mm diagnosed in LUMC and EMC between January 2000 and December 2007 and treated either with Ru-106, SRT or enucleation, or were sent to a center for proton beam radiation in (PSI, Villigen, Switzerland). For measuring tumor prominence ultrasound B-scans were used. Patients were excluded when metastases were present at diagnosis, or when patients had received treatment elsewhere before.

In this retrospective study we wanted to make both patient groups treated with Ru-106 and SRT comparable. For this we used an analysis based on expressed physician preference by the mathematical statistician Edward L. Korn [26]. In order to achieve comparability, all patient charts were depersonalized with regard to personal information, treatment center, treatment and results . From both LUMC and EMC an experienced ophthalmologist was consulted to assess these anonymous patient charts

and express their preference on how to treat each patient/melanoma. Both appraisers could choose one from all treatment options available: enucleation, ruthenium-106 brachytherapy, stereotactic radiotherapy and proton beam radiation.

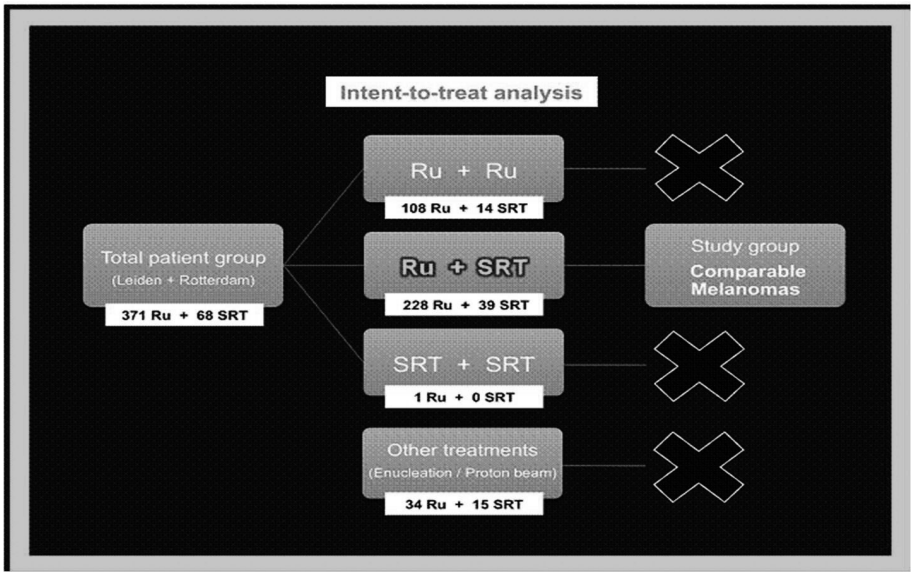
The tumors that were preferred to be treated with enucleation or proton beam radiation by one or both ophthalmologists were excluded, leaving patients with melanomas that were judged prognostically interchangeable: there was no strong indication for on specific treatment modality, and these tumors could have been treated with either Ru-106 and SRT, depending on the preference of the physician. When both appraisers preferred the same treatment (either both Ru-106 or SRT), the tumor was excluded. The original treatment of the final study group was used for a retrospective comparison of outcomes.
An ophthalmologist specialized in ocular melanomas used to work in EMC and transferred to LUMC in 2006. To prevent bias, we excluded this person in assessing the anonymous patient charts.

Treatment
Brachytherapy at LUMC was performed using Ruthenium-106 applicators manufactured by Bebig (Echet & Ziegler Eckert & Ziegler BEBIG GmbH, Berlin, Germany). Doses of 400 to 600 Gy combined with transpupillar thermotherapy (TTT), or 600 to 800 Gy without TTT were given. The dose was prescribed at the scleral surface and standardized to a dose of 100 Gy per 24h by using a correction factor [22]. For treatments after Jan 1, 2008, the dose was specified at the maximum prominence (130 Gy), and TTT was only used for insufficient regression.
Stereotactic radiotherapy at EMC was given on a linear accelerator with a stereotactic immobilization device. A treatment plan was made using stereotactic arcs of 6 MV photons (Xknife RT™ 1.03 Radionics). A total dose of 50 Gy was delivered in 5 fractions on 5 consecutive days. Treatment details have been described in previous publications [19,25,27].

Statistics
Primary endpoints were overall survival (OS) and metastatic-free survival (MFS) after 5 years, and percentage of secondary enucleations.

We used the Kaplan Meier to analyze survival. The survival outcomes were compared using Log Rank tests. For the comparison of the enucleation data the Chi Square test was used.

FIGURE 1 *Diagram of patient selection*



Results

The initial patient group, after excluding all enucleation and proton beam radiation treated patients, consisted of 371 patients treated with Ru-106 and 68 with SRT. After limiting the analysis to patients for whom a different preference was expressed, 228 Ru-106 patients (105 female, 123 male) and 39 SRT patients (21 female, 18 male) were included in the study (Figure 1). Median age was 62 years for the Ru-106 group and 66 for the SRT group; median tumor diameter was 11.5 mm and 11.1 mm, and median tumor prominence was 4.6 mm and 5.1 mm for the patients treated with Ru-106 and SRT, respectively (Table 1).

TABLE 1 *General Data and Tumor Characteristics*

Characteristics	Ru-106 Median	(range)	N[a]	SRT Median	(range)	N[b]	p
Age *(years)*	62	(29-83)		66	(48-83)		0.11
Gender							0.37
Male			123			18	
Female			105			21	
Follow-up *(months)*	63	(9-120)		51	(7-116)		0.02
Size *(mm)*							
Diameter	11.5	(6.7-15.5)		11.1	(7.7-15.6)		0.35
Tumor thickness	4.6	(2.5-7.9)		5.1	(3.2-7.6)		0.04

[a] Total number of patients is 228
[b] Total number of patients is 39

The 5-year OS showed no significant difference between the Ru-106 and the SRT groups: 76.6% versus 77.4% (p=0.37, Figure 2), nor did the 5-year MFS: 80.3% versus 82.3% for Ru-106 and SRT, respectively (p=0.59, Figure 3). Twenty-two patients (9.6%) treated with Ru-106 were enucleated versus 6 patients (15.4%) treated with SRT (p=0.36). The reasons for enucleation are listed in Table 2. For patients treated with Ru-106 local recurrences were the most frequent reason for enucleation, while this was toxicity for patients treated with SRT.

FIGURE 2 *Kaplan Meier curve of overall survival*

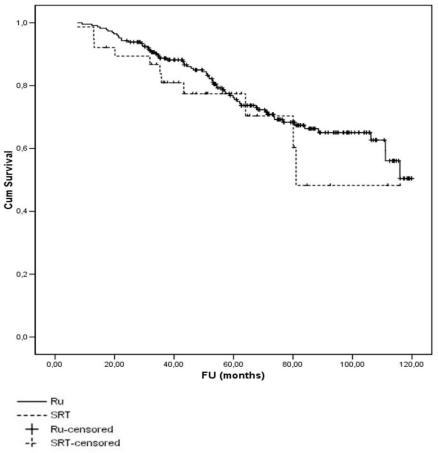


FIGURE 3 *Kaplan Meier curve of metastatic free survival*

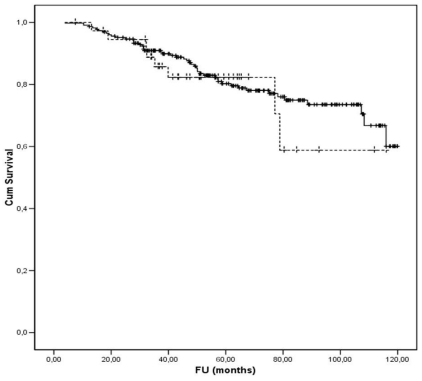


TABLE 2 *Causes of Enucleation*

Description	Ru-106	SRT
Local recurrence	12	2
Toxicity	6	4
Unknown	4	
Total[a]	22	6

[a] Absolute number of patients

Discussion

Brachytherapy with Ruthenium-106 applicators and stereotactic radiotherapy have both been developed to treat choroidal melanomas while preserving the eye both cosmetically and functionally. Indications for both treatment modalities overlap; in this study both modalities were compared.

We found no differences concerning the 5 year overall and metastatic free survival rates between Ru-106 and SRT. Our survival outcomes correspond well to known literature. In the COMS trial, the 5-year OS was 81% after treatment with I-125 brachytherapy; the metastastic rate was 10% after 5 years and 21% after 12 years [2,7]. Others reported 5-year OS rates of 77-88% for brachytherapy [5,6,28-30] and 82% for stereotactic radiotherapy [20]. 5-year MFS rates vary from 83% to 91% for brachytherapy and from 74% to 80% for SRT [5,12,31].

It should be noted, however, that the follow-up time of the patients treated with SRT was substantially shorter than for those treated with Ru-106. Moreover, metastases from choroidal melanomas can develop rather late [7,32,33]. Therefore, a subsequent analysis is planned after a few more years to determine differences in long-term outcome between these two treatments.

In our series, the rates of enucleation were not significantly different between the Ru-106 and the SRT groups, although numbers were small and a trend for more enucleations in the SRT group was found. Brachytherapy is known to be effective, with long-term tumor recurrence rates varying from 4 to 15% [3,6,34-36] [22]. A previous analysis from our group showed a satisfactory low recurrence rate of 4%, with 96% eye preservation [22]. For SRT, data are similar (91-98% local control), but published data have shorter FU [16,19-21]. However, these numbers are small and median follow-up is relatively short. Longer follow-up will provide more accurate information on outcomes after SRT. The most

important cause of enucleation differed, for Ru-106 this was local recurrence (5% of all Ru-106 patients), while for SRT this was toxicity (10% of SRT patients). However, these numbers are too small to draw firm conclusions. In future, with more patients and longer FU we will establish final comparisons of the rates of preserved visual acuity, complications and enucleations.

It is difficult to compare the results between these treatment modalities (Ru-106 and SRT) to literature data, because comparative studies of brachytherapy versus SRT have not been published previously, except for one abstract [37]. Moreover, virtually all published data are based on retrospective studies. In order to achieve the best comparability between both patient groups retrospectively, we used an analysis based on expressed physician preference [26].

Conclusion

With a new analysis method based on expressed physician preference, we have been able to compare patient groups treated with Ru-106 and with SRT in a retrospective manner. No significant differences were found in 5y-OS, 5y-MFS and rates of secondary enucleations for patients treated with Ru-106 compared with SRT. A second analysis is planned after longer follow-up, to determine the differences in MFS, side effects and visual acuity after treatment.

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Chapter 7

SUMMARY AND FUTURE PERSPECTIVES

Summary

Uveal melanomas can develop in any part of the uveal tract, but mostly they arise in the choroidea (1). Traditionally, uveal melanomas are treated by enucleation of the affected eye. During the last decades, various eye sparing treatment modalities have been developed. Depending on tumor location, size and patient characteristics the optimal treatment modality can be selected. For large sized melanomas, external beam radiation therapy with photons or heavy particles is being introduced in clinic (2-8). Treatment with external beam radiation therapy is complicated since the adjacent critical structures in and around the eye are more sensitive to irradiation than melanomas. The use of photon irradiation was first published in 1987 (9), presenting treatment by a single fraction using a stereotactic device (radio surgery). Although the local control rate was good, a substantial number of patients developed serious side effects, with the most important disadvantage of radiosurgery being the loss of sparing if critical structures are adjacent to the tumor, resulting in an enhanced complication probability. Fractionated stereotactic radiotherapy (fSRT) allows for delivery of an equivalent effective dose to the tumor combined with reduced effective dose in the surrounding tissues.However, fractionating the dose requires a noninvasive relocatable frame.

In this thesis, the development and feasibility of fSRT with a relocatable stereotactic frame is described. Also, the clinical outcome of fractionated SRT of uveal melanomas is reported. In 1999, a longitudinal cohort study was initiated in our institute, in order to study both the efficacy and the safety of fSRT for choroideal melanomas. A total dose of 50 Gy in 5 fractions (on 5 consecutive days) was given on a LINAC with a stereotactic device.

In **chapter 2** the development, feasibility and reliability of a patient friendly eye fixation device, attached on relocatable stereotactic frame is described. A plastic (PVC™) eye fixation construction, containing a blinking light and a camera, was attached to the Gill Thomass Cosman frame (GTC frame™, Radionics, Burlington, USA). The blinking light (fibre-glass connected to an LED*)* is positioned in front of the healthy eye. The camera is positioned at a distance of 20 cm from the affected eye to verify its position by checking the circumference of the eye contours and iris. In order to analyse the repositioning accuracy (RA), 2 CT scans were performed of each patient, with the affected eye in treatment position: one planning CT scan (before treatment) and a second CT scan

after completion of the therapy. The translations and rotations of the affected eye balls were calculated. Nineteen irradiated eye melanoma patients were analyzed. The average translations of the affected eyes were 0.1 +/- 0.3 mm, 0.1 +/- 0.4, and 0.1 +/- 0.5 mm, respectively. The median rotation of the diseased eye was 8.3 degrees. These movements are all within the applied margin of 2 mm from the target volume (GTV) to the planning treatment volume (PTV). It can be therefore concluded that the eye fixation device is an adequate and reliable system for eye melanoma patients treated with a relocatable stereotactic frame.

The early effectiveness and acute side effects of fSRT in uveal melanomas are studied in **chapter 3**. In this prospective, nonrandomized clinical trial 38 patients were analyzed. Primary endpoints were local control, best corrected visual acuity (BCVA) and acute toxicity. The mean follow-up (FU) was 25 months (10-36 months). During this FU, no recurrences were seen. The BCVA declined from a mean of 0.21 at diagnosis to 0.06 two years after therapy. After an initial decline, the BCVA in most anterior located tumors recovered. The BCVA found in the posterior located tumors however was permanent. The most common acute side effects were mild conjunctival symptoms, loss of hair or lashes and fatigue. One patient underwent an enucleation 2 months after irradiation, because of total retinal detachment and massive inflammation. In conclusion, fSRT of uveal melanoma was well tolerated and resulted in excellent local control. The BCVA two years after therapy was however disappointing, mainly because of the considerable tumor size and the location of tumor. Obviously, larger number of patients and a prolonged FU were needed for long-term local control, late toxicity and survival.
In **chapter 4** long term local control, late side effects and survival are evaluated. The clinical outcome of 102 patients were analyzed; the median FU was 32 months. Local control was achieved in 96% of the patients; 4 patients had to be enucleated due to local tumor progression after a median FU of 40 months (14-85 months). Because of failure of downsizing of the tumor, 6 patients underwent transpupillar thermotherapy. Ten patients developed cataract grade 3; the development of cataract turned out to be dose dependent: a median dose of 5 Gy/fraction in the lens and ciliary body caused a cataract in 50 percent of the cases. Severe retinopathy and opticoneuropathy grade 3 or 4 occurred in 19 and 13 patients, respectively. For opticoneuropathy a dose dependency was found (TD50 of maximum dose in the optical nerve was 9.6 Gy/fraction). Before therapy, 57 patients had retinal detachment (RD). Eventually, 2 years

post-treatment, RD resolved in all patients, but 2: These 2 patients who developed RD grade 4, had to be enucleated (1 because of secondary endophthalmitis after vitrectomy). Larger melanomas and the existence of grade 2 or 3 RD before treatment appeared to be prognostic predicting factors for the development of grade 3 and 4 RD. Eight patients out of 9 who developed grade 3 or 4 neovascular glaucoma (NVG) had to be enucleated. Tumor thickness and the appearance of grade 3 retinopathy were predicting factors for the development of NVG. Sixteen patients died, corresponding to a 5-year overall survival (OS) of 77% (SE 6%); the 5-year melanoma-specific survival (MSS) rate was 83% (SE = 5%). Fourteen patients developed distant metastases (5-year MFS 75%). In all cases the liver was affected. In total, 15 patients were enucleated, 2 to 85 months after radiation, which leads to a 5-year enucleation-free survival of 66%.
The radiosensitivity of the lacrimal gland in uveal melanoma patients is pointed out in **chapter 5**. The goal of this paper was to find a dose volume effect for (inhomogeneous) irradiated lacrimal glands. For this purpose, the development of a dry eye syndrome (DES) and the course of tear production of 72 irradiated patients were analyzed and related to the dose in the lacrimal glands. We found a dose volume relationship of irradiated lacrimal glands with regard to the appearance of DES and to reduced tear production. A median dose of 7 Gy/fraction to the lacrimal gland caused a 50 percent chance of low Schirmer results; a median dose of 10 Gy corresponded to a 50 percent probability of DES. In conclusion, there is a clear dose volume relationship of irradiated lacrimal glands with regard to reduced tear production and the appearance of DES.

In conclusion, fSRT is an efficient and safe treatment modality for uveal melanomas. However, the visual acuity after treatment is disappointing and the number of secondary enucleations is substantial. It is known that clinical outcome of treatment of uveal melanomas is depended on tumor and patient characteristics. This complicates the comparison of our data to literature. It is therefore of interest to compare our data with equal tumor and patient characteristics treated with other eye sparing modalities (and enucleation). In **chapter 6** the data of patients with medium sized tumors (i.e. 2-8 mm) treated with fSRT (68 patients) in the Erasmus MC were compared to patients with similar characteristics treated with ruthenium brachytherapy (371 patients) in LUMC (Leiden). The comparison was achieved according to a retrospectively performed intention to treat analysis. After the intention to treat analysis, 367 patients (228 Ru, 39 fSRT) were suitable for the comparison. No significant differences were found in overall survival, metastatic-free survival and secondary enucleation rate.

Future perspectives

Tumor definition

For the sake of both better organ sparing and higher local tumor control, an excellent tumor definition is warranted. In some cases, the delineation of the tumor on the planning CT and MRI was difficult, due to the position of the tumor (i.e. cranially or caudally in the globe) and/ or the unclear demarcation of the tumor. Uveal melanomas are best visualized on ultrasonography. The development and implementation of software that matches images of 3D sonography with the planning CT scan could fix this problem for a major part. The matching of the MRI with the CT scan was often complicated because of the different gaze directions in both scans. Besides, the eye globe was sometimes substantially deformed. This problem could be (partly) solved with an MRI compatible eye fixation device, which is currently under development. Also, the technique of the MRI can be improved (10, 11).

Toxicity

The outcome of visual acuity was disappointing, especially in posterior located tumors. Also, the number of enucleations due to toxicity was substantial.

The most important reason for enucleation is the occurrence of NVG. Hopefully, if we can get a better comprehension in the pathophysiology and development of NVG, we can reduce it.

Comparison of treatment modalities

Like ours, published data of treatment of uveal melanomas are mostly nonrandomized small clinical trials (2, 4, 7, 8, 12-23). It is of interest to compare our data set with similar tumor and patient characteristics treated with other eye sparing modalities and/or enucleation. We performed an analysis in which patients treated with fSRT had comparable results in survival and secondary enucleations with respect to similar patients treated with brachytherapy. Comparison of local control, toxicity and visual acuity of these groups will be executed in near future.

Also, planning studies using different treatment modalities should be performed in order to analyze the best treatment option for various melanoma sizes and locations (24).

Treatment developments

Future research should be aimed to improve the existing treatment techniques and to prolong the FU of new treatment techniques with as ultimate goal the reduction of treatment related morbidity and the improvement of local tumor control and functional outcome (25).

Another explanation for local tumor failure could be the variability in intrinsic radiation sensitivity of uveal melanomas (26-28). With a better understanding of the radiation sensitivity it is probably possible to identify the group of patients that benefits of radiation.

Quality of life

Since enucleation and eye sparing treatment modalities have comparable survival results, improvement of the quality of life (QoL) should be an important goal in eye sparing treatment modalities. Especially with the substantial number of secondary enucleations and the disappointing results in BCVA, the QoL after treatment with fSRT is of major importance. For brachytherapy, published papers showed no large differences in quality of life, patients treated with brachytherapy are more vital and have slightly better visual results but were also more anxious when compared to patients treated with enucleation (29-33). All uveal melanoma patients treated between 1999 and 2008 at the Erasmus MC (with fSRT or enucleation) filled in QoL questionnaires. These data will be analyzed and reported in the near future.

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Chapter 8

SAMENVATTING EN TOEKOMSTPERSPECTIEF

Samenvatting

Oogmelanomen kunnen zich in ieder onderdeel van de tractus uvealis ontwikkelen, maar ze komen het meest frequent in de choroidea voor (1). Van oudsheris enucleatie van het aangedane oog de behandeling voor oogmelanomen. In de afgelopen decennia zijn er echter verschillende oogsparende behandelmodaliteiten ontwikkeld. Afhankelijk van de tumorlocatie, de tumorgrootte en de patiëntenkenmerken kan de meest optimale behandeling worden gekozen. Voor grote tumoren is er uitwendige radiotherapie met fotonen dan wel zware partikels (2-8). Behandeling met uitwendige radiotherapie is een uitdaging omdat de aangrenzende kritieke structuren in en om het oog gevoeliger zijn voor bestraling dan het oogmelanoom zelf. Het onderzoek zoals beschreven in dit proefschrift heeft zich gericht op uitwendige radiotherapie met fotonen. De behandeling middels uitwendige radiotherapie met fotonen is voor het eerst gepubliceerd in 1987 (9). In deze publicatie werd een behandeling met radiochirurgie beschreven. Hierbij werd een eenmalige dosis gegeven met behulp van een stereotactisch bestralingsapparaat. Alhoewel de lokale controle goed was, ontwikkelde een substantieel deel van de patiënten ernstige bijwerkingen. Het belangrijkste nadeel van de radiochirurgie is de relatief hoge (eenmalige) bestralingsdosis die in de aangrenzende kritieke structuren wordt afgegeven. Dit resulteert in een groter risico op complicaties. Met behulp van gefractioneerde stereotactische radiotherapie (fSRT) kan de bestralingsdosis in delen gegeven worden. Hiermee kan de tumor met een equivalent effectieve dosis worden bestraald, terwijl de aanliggende structuren beter kunnen worden gespaard. Echter, als de dosis in meerdere fracties wordt gegeven is een niet-invasief en herbruikbaar bestralingsframe vereist.

In dit proefschrift wordt de ontwikkeling en de haalbaarheid van fSRT met een niet-invasief en herbruikbaar stereotactisch frame beschreven. Daarnaast worden de klinische resultaten van de behandeling met fSRT voor oogmelanomen gerapporteerd. In 1999 werd er in het Erasmus MC een longitudinale cohortstudie gestart om de werkzaamheid en de veiligheid van een behandeling met fSRT voor oogmelanomen te onderzoeken. Hierbij werd er een dosis van 50 Gy gegeven, verdeeld in 5 fracties van 10 Gy (op 5 achtereenvolgende dagen). De bestraling werd gegeven op een lineaire versneller speciaal geschikt voor stereotactische radiotherapie.

In **hoofdstuk 2** wordt de ontwikkeling, haalbaarheid en betrouwbaarheid van een patiëntvriendelijk oogfixatiesysteem, wat bevestigd kan worden aan een bestaand herbruikbaar stereotactisch frame beschreven. Het onderzoek is als volgt gedaan: een plastic (PVC™) oogfixatieconstruktie, bestaande uit een knipperend lampje en een camera, werd bevestigd aan het Gill Thomass Cosman frame (GTC frame™, Radionics, Burlington, USA). Het lampje (fiberglas met een LED) wordt voor het gezonde oog geplaatst. De camera bevindt zich 20 cm voor het aangedane oog en filmt het aangedane oog. Door de oogcontouren en de contour van de iris te controleren, wordt de positie van het aangedane oog geverifieerd.
De herpositioneringsnauwkeurigheid werd geanalyseerd met behulp van een 2-tal CT-scans van iedere patiënt. Hierbij was het oog in de behandelpositie: één CT-scan werd gemaakt voorafgaand aan de behandeling en ten behoeve van de planning. De tweede scan werd na de behandeling gemaakt. De behaalde resultaten waren als volgt: van 19 bestraalde oogmelanoompatiënten werden de verplaatsingen en rotaties van de aangedane ogen berekend en geanalyseerd. De gemiddelde verplaatsingen van de aangedane ogen waren respectievelijk 0.1 +/- 0.3 mm, 0.1 +/- 0.4, en 0.1 +/- 0.5 mm. De mediane rotatie van het zieke oog was 8.3 graden. Deze verschuivingen waren allemaal binnen de toegepaste marge van 2 mm rondom het doelvolume (GTV) naar het 'planning treatment volume' (PTV). Hiermee kan worden geconcludeerd dat het oogfixatiesysteem een adequaat en betrouwbaar systeem is voor de fSRT-behandeling van oogmelanomen.

De vroege resultaten en de acute bijwerkingen van fSRT voor oogmelanomen zijn beschreven in **hoofdstuk 3**. In deze prospectieve, niet-gerandomiseerde klinische trial werden 38 patiënten geanalyseerd. De primaire eindpunten waren lokale controle, de gecorrigeerde visus ('best corrected visual acuity' (BCVA)) en de acute toxiciteit. De gemiddelde follow-up (FU) was 25 maanden (10-36 maanden). Tijdens deze FU werden er geen lokale recidieven gezien. The BCVA nam af van een gemiddelde van 0.21 gemeten bij de diagnose naar 0.06 twee jaar na de behandeling. Bij de meeste anterior gelegen tumoren herstelde de BCVA zich enigszins. Bij de posterior gelegen tumoren was de afname in BCVA permanent. De meest voorkomende acute bijwerkingen waren milde symptomen van de conjunctiva, verlies van haar of wimpers en vermoeidheid. Bij één patiënt werd het aangedane oog 2 maanden na de bestraling geënucleëerd, omdat er sprake was van een totale netvliesloslating in combinatie met een uitgebreide

ontstekingsreactie. Concluderend werd de behandeling met fSRT voor oogmelanomen goed getolereerd en was de lokale controle na een korte FU uitstekend. De BCVA was na 2 jaar FU echter teleurstellend. Voor lokale controle op lange termijn, late toxiciteit en overleving zijn grotere patiëntenaantallen en een langere FU nodig .

In **hoofdstuk 4** worden de lokale controle op lange termijn, de late toxiciteit en de overleving beschreven. Hiervoor werd de klinische uitkomst van 102 patiënten geanalyseerd; de mediane FU van deze groep was 32 maanden. Bij 96% van de patiënten werd lokale controle van het oogmelanoom bereikt; 4 patiënten moesten, na een mediane FU van 40 maanden (14-85 maanden), worden geënucleëerd vanwege lokale tumorprogressie. Zes patiënten ondergingen transpupillaire thermotherapie, omdat de tumor niet snel genoeg in grootte afnam. Tien patiënten ontwikkelden een graad 3 cataract. Het ontstaan van cataract bleek uit onze analyse dosisafhankelijk te zijn: wanneer er een mediane dosis van 5 Gy/fractie in de lens en het corpus ciliare kwam, veroorzaakte dat in 50% van de patiënten een cataract. Ernstige retinopathie en opticoneuropathie graad 3 en 4 trad op bij respectievelijk 19 en 13 patiënten. Ook de kans op het optreden van ernstige opticoneurpathie was afhankelijk van de dosis (TD50 van de maximum dosis in de n opticus was 9.6 Gy/fractie). Bij de diagnose van het oogmelanoom hadden 57 patiënten een ablatio retinae. Twee jaar na de behandeling was deze ablatio bij alle patiënten hersteld, met uitzondering van 2 patiënten met een graad 4 ablatio retinae, die allebei een enucleatie ondergingen (1 van deze 2 patiënten onderging een enucleatie vanwege een secundaire endophthalmitis na vitrectomie). Prognostisch voorspellende factoren voor de kans op de ontwikkeling van een graad 3 of 4 ablatio retinae waren de grootte van de tumor (grotere tumoren gaven een grotere kans) en de aanwezigheid van graad 2 of 3 ablatio retinae bij diagnose. Van de 9 patiënten die een graad 3 of 4 neovasculair glaucoom (NVG) ontwikkelden, moesten er uiteindelijk 8 een enucleatie ondergaan. Voorspellende factoren voor het ontwikkelen van NVG waren de tumordikte en het optreden van graad 3 retinopathie.
Er overleden 16 patiënten, wat overeenkomt met een 5-jaars overleving van 77% (SE 6%); de 5-jaars melanoomspecifieke overleving (MSS) was 83% (SE = 5%). Veertien patiënten kregen afstandsmetastasen (5-jaars metastasenvrije overleving van 75%). Bij alle 14 was ook de lever aangedaan. In totaal werd bij 15 patiënten het aangedane oog geënucleëerd, variërend van 2 tot 85 maanden na de radiotherapie, overeenkomstig met een 5-jaars enucleatievrije overleving van 66%.

De stralingsgevoeligheid van de traanklier bij oogmelanoompatiënten wordt beschreven in **hoofdstuk 5**. Het doel van het onderzoek, dat beschreven is in dit artikel, was om een dosis-volume effect te vinden voor (inhomogeen) bestraalde traanklieren. Hiervoor werden zowel het optreden van droge ogen (dry eye syndrome (DES)) als het verloop van de traanproduktie van 72 bestraalde patiënten geanalyseerd. Er werd een dosis-volume verband gevonden ten aanzien van zowel de kans op het krijgen van DES als op de afname van de traanproduktie en de dosis in de traanklier. Een mediane dosis van 7 Gy/fractie gegeven aan de traanklier veroorzaakte een kans van 50 procent op verminderde traanproduktie; een mediane dosis van 10 Gy correspondeerde met een kans van 50% op het krijgen van DES. Concluderend was er een duidelijke dosis-effect-relatie tussen de dosis die de traanklier had gekregen versus de verminderende traanproduktie en het optreden van DES.

Uit de bovenstaande hoofdstukken kan geconcludeerd worden dat fSRT een efficiënte en veilige behandeling is voor oogmelanomen. De visus na behandeling is echter teleurstellend en ook het aantal secundaire enucleaties is substantieel. De klinische uitkomst van de behandeling van oogmelanomen is afhankelijk van zowel tumor- als patiënteneigenschappen. Dit compliceert het vergelijken van onze data met de bestaande literatuur. Het zou interessant zijn om onze data te kunnen vergelijken met andere oogsparende behandelingsmodaliteiten (en enucleatie) met vergelijkbare tumor- en patiëntenkarakteristieken. In **hoofdstuk 6** werd de data van 68 patiënten met oogmelanomen van een gemiddelde grootte (i.e. 2-8 mm), die behandeld zijn met fSRT in het Erasmus MC (Rotterdam) vergeleken met 371 vergelijkbare patiënten, die behandeld zijn met ruthenium brachytherapie (Ru) patiënten in het LUMC (Leiden). De groepen werden vergeleken met behulp van een retrospectief uitgevoerde 'intention-to-treat' analyse. Na deze analyse waren er 367 patiënten (39 fSRT, 228 Ru) geschikt voor de vergelijking van beide behandelingen. Hierbij werd er geen verschil gevonden in de overleving (overall survival en metastastic-free survival) noch in de aantallen secundaire enucleaties.

Toekomstperspectief

Tumordefinitie

Zowel voor betere sparing van de gezonde weefsels als voor betere lokale tumorcontrole is een uitstekende afbeelding van de tumor noodzakelijk. Intekening van de tumor op de plannings-CT-scan en de gematchte MRI-scan werd soms bemoeilijkt door de ligging van de tumor (i.e. craniaal of caudaal in de oogbol gelegen tumoren) en/of door de matige afgrensbaarheid van de tumor. Oogmelanomen zijn het best zichtbaar op een ECHO. De ontwikkeling en implementatie van software die de 3D ECHO-afbeeldingen kan matchen met de CT-scan kan een groot deel van dit intekenprobleem oplossen. De matching van de MRI- met de CT-scan werd bemoeilijkt doordat de kijkrichting van de beide scans verschilde. Daarnaast was de oogbol op de MRI in sommige gevallen substantieel vervormd. Door een oogfixatiesysteem te gebruiken dat ook geschikt is voor de MRI zou een deel van het probleem kunnen worden opgelost. Dit systeem is momenteel in ontwikkeling. Verder kan de techniek van de MRI worden verbeterd (10, 11).

Toxiciteit

De uitkomst van de visus was teleurstellend, vooral voor de posterior gelegen tumor. Bovendien was het aantal enucleaties dat verricht moest worden ten gevolge van de toxiciteit substantieel. De belangrijkste reden voor deze enucleaties was het optreden van NVG. Hopelijk krijgen we in de toekomst meer inzicht in de pathofysiologie en in de ontwikkeling van NVG, zodat we dit kunnen verbeteren.

Vergelijking van de behandelingsmodalitieiten

Net zoals onze data, zijn de meeste publicaties over de behandeling van oogmelanomen niet-gerandomiseerde kleine klinische trials (2, 4, 7, 8, 12-23). Het zou interessant zijn om onze uitkomsten van fSRT voor oogmelanomen te kunnen vergelijken met patiënten met vergelijkbare tumor- en patiëntkarakteristieken die behandeld zijn met andere oogsparende behandelmodaliteiten en/of enucleatie. We hebben een vergelijkende analyse uitgevoerd, waarbij bij patiënten die behandeld zijn met fSRT en met brachytherapie vergelijkbare resultaten waren te zien ten aanzien van overleving en secundaire enucleatie. Binnenkort zullen lokale controle, toxiciteit en visus van beide groepen met elkaar vergeleken worden. Bovendien zullen planningsstudies, waarbij

de verschillende bestralingsmodaliteiten met elkaar vergeleken worden, ons meer duidelijkheid moeten geven over de meest optimale behandeloptie voor verschillende tumorafmetingen en –locaties (24).

Ontwikkeling van nieuwe behandelingen

Toekomstig onderzoek moet gericht zijn op het verbeteren van de bestaande behandelingstechnieken met als doel het verminderen van behandelingsgerelateerde morbiditeit en het verbeteren van de lokale tumorcontrole en de functionele uitkomst (25). Bovendien is er een langere FU nodig van de patiënten die behandeld zijn met nieuwe behandelingstechnieken. Een andere verklaring voor het falen van lokale tumorcontrole zou de variabiliteit in intrinsieke radiosensitiviteit van oogmelanomen kunnen zijn (26-28). Door een beter begrip van de radiosensitiviteit is het wellicht mogelijk om patiëntengroepen te kunnen identificeren die gevoelig zijn voor radiotherapie.

Kwaliteit van Leven

Aangezien enucleatie en oogsparende behandeltechnieken vergelijkbare overlevingsresultaten hebben, zou verbetering van de Kwaliteit van Leven (KvL) een belangrijk doel moeten zijn voor (nieuwe) oogsparende technieken. Het relatief grote aantal secundaire enucleaties en de teleurstellende resultaten in de BCVA, maakt onderzoek naar de KvL na behandeling met fSRT nog belangrijker. Publicaties over KvL na brachytherapie lieten geen grote verschillen zien. Patiënten behandeld met brachytherapie zijn vitaler en hebben iets betere visusresultaten, maar waren ook angstiger vergeleken met patiënten die behandeld waren met enucleatie (29-33). Alle oogmelanoompatiënten die behandeld zijn tussen 1999 en 2008 in het Erasmus MC (met fSRT of enucleatie) hebben KvL- vragenlijsten ingevuld. Deze data zullen binnenkort worden geanalyseerd en gepubliceerd.

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Muller K, Naus N, Nowak PJ, Schmitz PI, de Pan C, van Santen CA, Marijnissen JP, Paridaens DA, Levendag PC, Luyten GP. Fractionated stereotactic radiotherapy for uveal melanoma, late clinical results. *Radiother Oncol. 2012 Feb;102(2):219-24. Epub 2011 Aug 22.*

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CURRICULUM VITAE

Karin Muller werd geboren op 22 mei 1974 te Hardenberg. Na het behalen van het VWO-diploma in 1992 op het Dollard College te Winschoten, begon ze aan haar studie Geneeskunde aan de Rijksuniversiteit te Groningen. Tussen haar doctoraal en haar co-schappen in, heeft ze enkele maanden wetenschappelijk onderzoek gedaan naar de resistentie van malariamuggen in Kisumu (Kenia). In december 1998 behaalde zij haar artsexamen met genoegen.

In 1999 werkte zij als arts-assistent (niet in opleiding) interne geneeskunde in het toenmalige Zuiderziekenhuis, tegenwoordig onderdeel van het Maasstad Ziekenhuis in Rotterdam. Hier werd de kiem gelegd voor haar verdere loopbaan in de oncologie.

In februari 2000 begon zij als AGNIO op de afdeling radiotherapie in het Erasmus MC, waar zij in januari 2001 startte met de opleiding tot radiotherapeut-oncoloog (opleider Prof.dr. P.C. Levendag). Tijdens haar opleiding begon zij aan haar onderzoek, aanvankelijk gericht op hoofd-halstumoren en sinds 2003 op uveamelonomen, zoals gepubliceerd in dit proefschrift. Het onderzoek over stereotactische radiotherapie bij uveamelanomen werd, mede onder begeleiding van Dr. P. Nowak, verricht in nauwe samenwerking met de afdeling oogheelkunde (Dr. G. Luijten) van het Erasmus MC. Na het afronden van haar opleiding tot radiotherapeut-oncoloog in 2007, heeft ze enige tijd als staflid gewerkt in het Erasmus MC. Hierbij heeft zij zich onder andere toegelegd op stereotactische radiotherapie.

Sinds december 2008 werkt ze als radiotherapeut-oncoloog in het Radiotherapeutisch Instituut Stedendriehoek en Omstreken (RISO) te Deventer. Als specifieke aandachtsgebieden heeft zij de behandeling van gastro-intestinale tumoren, haematologische maligniteiten en mammacarcinomen. Onder haar supervisie is in het RISO de stereotactische radiotherapie voor levermetastasen opgezet. Bovendien heeft ze meegewerkt aan het opzetten van het Oncologisch Centrum Deventer, in samenwerking met het Deventer Ziekenhuis.