Aus der Klinik für Augenheilkunde
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DISSERTATION

Radiation Retinopathy and Optic Neuropathy after Proton Beam Therapy of Choroidal Melanoma – A Retrospective Analysis of the Incidence, Predictive Factors and Visual Outcome

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List of abbreviations

Avg = Average

BAP-1 = Breast Cancer-Associated Protein 1

CF = Counting Fingers

CGE = Cobalt Gray Equivalents

CI = Confidence Interval

Co = Cobalt

COMS = Collaborative Ocular Melanoma Study

CT = Computed Tomography

EDI-OCT = Enhanced Depth Imaging- Optical Coherence Tomography

Gy = Gray

HM = Hand Motion

I = Iodine

IVI = Intravitreal Injection

LINAC = Linear Accelerator

LogMAR = Logarithm of the Minimal Angle of Resolution

LP = Light Perception

MRI = Magnetic Resonance Imaging

mRNA = Messenger Ribonucleic Acid

NLP = No Light Perception

OCT = Optical Coherence Tomography

PRP = Pan-retinal Photocoagulation

PT = Proton Therapy

PVR = Proliferative Vitreoretinopathy

resp. = respectively

Rh = Rhodium

Ru = Ruthenium

SD-OCT = Spectral Domain- Optical Coherence Tomography

SRS = Stereotactic Radiosurgery

SRT = Stereotactic Radiotherapy

TNM = Tumor, Node, Metastases

TTT = Transpupillary Thermotherapy

UV = Ultraviolet

VA = Visual Acuity

VEGF = Vascular Endothelial Growth Factor

Abstract

Background: Radiation therapy of choroidal melanomas has replaced enucleation as the treatment of choice since metastasis and mortality rates were proven comparable. This development has shifted the focus more towards functional outcome due to the frequent occurrence of radiation-induced complications. Among them, radiation retinopathy and optic neuropathy are two of the major vision compromising complications.

Purpose: The aim of this retrospective study was to investigate radiation-induced retinopathy and optic neuropathy after proton beam irradiation in choroidal melanomas in a long-term follow-up with the focus on determining incidence rates, risk factors and visual prognosis.

Methods: We evaluated 1085 patients with choroidal melanomas who received proton beam therapy with a total dose of at least 60 cobalt gray equivalents (CGE) as primary tumor treatment at the Department of Ophthalmology of the Charité - Universitätsmedizin Berlin in cooperation with the Helmholtz-Center Berlin between June 1998 and December 2013. Excluded were all patients with a follow-up of less than 12 months and patients who underwent tumor resection or endodrainage vitrectomy. Data were obtained from an existing data base and by reviewing electronic records and statistically analyzed using SPSS.

Results: The mean follow-up was 54.4 months (12.0 – 170.4 months). 790 patients (72.8%) developed radiation retinopathy after a mean latency of 23.0 months (1.4 – 99.8 months) and 472 patients (43.5%) developed optic neuropathy after a mean latency of 25.6 months (0.2 – 125.7 months) since proton radiotherapy. Initial mean visual acuity was 0.3 logMAR dropping to final visual results of 0.5 logMAR in complication-free patients, 1.0 logMAR if solely retinopathy had been diagnosed or 1.5 logMAR in patients with diagnosed optic neuropathy. Tumor distance to the equator and its proximity to the optic disc, as well as radiation dose on fovea and optic disc were identified as significant predictive factors for the appearance of optic neuropathy. The relative risk of the development of optic neuropathy increased sharply and linearly with the dose on the optic disc. For radiation retinopathy, tumor distance to the equator was the sole significant determinant of its manifestation, with a higher risk attributable to centrally located tumors.

Conclusion: Radiation-induced retinopathy and optic neuropathy are very frequently occurring complications after proton beam radiotherapy of choroidal melanomas and visual impairment is common and pronounced especially in optic neuropathy. Patients with high-risk tumors as defined by tumor location should be informed about their risk of complication and visual prognosis.

Zusammenfassung

Hintergrund: Aufgrund vergleichbarer Metastasierungs- und Mortalitätsraten hat die bulbuserhaltende Bestrahlung die Enukleation als Therapie der Wahl bei Aderhautmelanomen abgelöst. Folge dieser Entwicklung sind häufigere Strahlenkomplikationen und damit einhergehend ein stärkerer Fokus auf das funktionelle Therapieergebnis. Die Strahlenretinopathie und Strahlenoptikopathie gehören hierbei zu den bedeutsamsten Komplikationen, aufgrund der damit assoziierten teilweise massiven Visuseinschränkungen.

Studienziel: Das Ziel dieser retrospektiven Studie war die Untersuchung der Langzeitergebnisse von Aderhautmelanomen nach Protonentherapie im Hinblick auf die Inzidenz der Strahlenretinopathie und Strahlenoptikopathie, ihrer Risikofaktoren und Visusprognose.

Methodik: In diese retrospektive Studie wurden 1085 Patienten mit einem Aderhautmelanom eingeschlossen, die im Zeitraum von Juni 1998 bis Dezember 2013 an der Augenklinik der Charité – Universitätsmedizin Berlin in Zusammenarbeit mit dem Helmholtz-Zentrum Berlin eine Protonenbestrahlung mit mindestens 60 CGE Gesamtdosis erhielten. Ausschlusskriterien waren ein Nachuntersuchungszeitraum von unter 12 Monaten und eine anschließende Tumorresektion oder Endodrainage mit Vitrektomie. Sämtliche Daten wurden von einer bestehenden Datenbank oder nach Durchsicht vorhandener elektronischer Akten erhoben und mit SPSS statistisch ausgewertet.

Ergebnisse: Die Nachbeobachtungszeit betrug im Mittel 54,4 Monate (12,0 – 170,4 Monate). 790 Patienten (72,8%) und 472 Patienten (43,5%) entwickelten eine Strahlenretinopathie bzw. Strahlenoptikopathie, im Mittel nach einer Latenzperiode von 23,0 Monaten (1,4 – 99,8 Monate) bzw. 25,6 Monaten (0,2 – 125,7 Monate) nach Bestrahlung. Der mittlere Visus fiel zum letzten Untersuchungszeitpunkt von initialen 0,3 logMAR auf Visuswerte von 0,5 logMAR bei Patienten ohne Strahlenkomplikation, 1,0 logMAR bei Manifestation lediglich einer Strahlenretinopathie und 1,5 logMAR bei diagnostizierter Strahlenoptikopathie. Als signifikante Risikofaktoren für die Entwicklung einer Strahlenoptikopathie konnten eine kurze Distanz des Tumors zum hinteren Augenpol und zur Papille identifiziert werden, sowie die applizierte Bestrahlungsdosis auf die Fovea und Papille. Das relative Risiko für das Auftreten einer Strahlenoptikopathie zeigte dabei einen steilen linearen Anstieg mit steigender Dosis auf die Papille. Das Risiko einer Strahlenretinopathie war besonders hoch in zentral gelegenen Tumoren,

die Tumorlage in Bezug zum Äquator die einzige signifikante Determinante dieser Komplikation.

Schlussfolgerung: Die Strahlenretinopathie und Strahlenoptikopathie sind häufige nach Protonenbestrahlung auftretende Komplikationen, die – besonders im Falle einer Strahlenoptikopathie – mit einer deutlichen Visuseinschränkung assoziiert sind. Patienten mit einem Hoch-Risiko-Tumor zentraler Lage sollten über ihr hohes Komplikationsrisiko und die damit verbundene schlechte Visusprognose informiert werden.

1. Introduction

1.1 Epidemiology of choroidal melanoma

Approximately 4% of all melanomas are intraocular or ocular adnexal tumors. About 80% of these are classified as uveal melanoma, comprising choroidal melanoma, ciliary body melanoma and melanoma primarily affecting the iris. Accounting for 90% of all uveal melanoma, choroidal melanoma are the most common intraocular tumor during adulthood, newly occurring in 5 per million people a year. Rates increase with higher age and children are rarely affected. Incidence differences between the sexes are small, with advancing age, men are slightly more often affected. There is no preferred site to be found, right eyes and left eyes are equally often the site of tumor manifestation [1-4].

15-year survival rates after choroidal melanoma diagnosis are still unchanged at about 50%, correlating with the development of metastases [5]. In approximately one third of the patients, metastases will be diagnosed in the course of 10 years after initial diagnosis of choroidal melanoma [6]. If metastases occur, they will primarily affect the liver via hematogenic spread. These patients' median survival is approximately 5-7 months [7-9]. Metastases are rarely already present at initial diagnosis of choroidal melanoma, occurring only in 2-3% of the patients [10, 11]. Primary lymphogenic metastasis into preauricular, submandibular or cervical lymph nodes has only been reported in isolated cases with extraocular extension of the melanoma [12-15]. The main risk factor for metastasis is a chromosome 3 loss, which is found to be highly correlated with a significant reduction of life expectancy due to death as a result of metastasis [16]. Alterations in chromosomes 6 and 8 are further genetic factors associated with significantly higher risk of developing metastasis [17]. Several more factors have been described to limit survival. These include clinical factors like tumor dimensions (especially basal tumor diameter), ciliary body involvement, extraocular spread or tumor stage as well as histological factors, among them the presence of epithelioid melanoma cells and closed loops [18-23].

1.2 Pathogenesis

A familial predisposition is a very rare explanation for the etiology of choroidal melanomas. Most choroidal melanomas develop de novo from melanocytes as well as retinal nevi, melanocytosis or melanocytoma [2]. Under the assumption that all choroidal melanomas arise from a nevus, the risk for uveal nevi to transform into a malignant entity is 1:8845, increasing

with advancing age. Factors that are said to confirm this transformation are a tumor thickness over 2 mm, subretinal fluid together with serous retinal detachment, orange pigment – an accumulation of lipofuscin on the tumor's surface –, tumor attachment to the optic disc and symptoms such as visual complaints [24, 25].

The relevance of sunlight exposure for the genesis of choroidal melanomas is not proven and still controversially debated [26, 27].

1.3 Symptoms

Choroidal melanomas usually grow gradually with a tumor doubling time of 154 to 511 days and may therefore stay unnoticed for a long time [28, 29]. Hence, these tumors are often diagnosed incidentally within the framework of an ophthalmologic routine examination. Early symptoms are generally due to a central location if the tumor affects the macula, the exudation of the tumor and the accompanying exudative retinal detachment, and possibly occur in dependence on position and activity as the liquid follows gravity. Patients may perceive reduced visual acuity, dark shadows or defects in the visual field, light flashes, vitreous opacity or metamorphopsia [30-33].

In progressed stages the tumor may cause impairments due to a growth in size and resulting moving of the optical axis or furthermore cataract, astigmatism, uveitis and neovascularization, glaucoma and thus pain [2].

1.4 Diagnosis

Besides taking into account possible symptoms in the patient's medical history, diagnosis of a choroidal melanoma is made mainly based on clinical examination with a slit lamp and indirect ophthalmoscope as well as ultrasonography of the eye [2].

Binocular indirect ophthalmoscopy allows detection and monitoring of clinical signs such as orange pigment, exudative retinal detachment and increasing size of the tumor in time. Full pupillary dilation is necessary to examine the entire fundus. Documentation of size, growth and location is achieved via digital photography, sometimes additionally using wide-angle photos for very large or peripheral melanomas [2, 34].

Ultrasonography displays the melanoma's characteristic low reflectivity in the A- and B-scan. Furthermore, it has its importance especially for measuring the size and thickness of the tumor. In B-scan, ultrasonography tumor configuration may be depicted, with a mushroom or collar

button shape being virtually pathognomonic for the choroidal melanoma. Moreover, ultrasonography of the eye is a highly sensitive and useful method for detecting extraocular tumor growth, which will show lower reflectivity than the normal orbital tissues [2, 35].

Fluorescein angiography may be used to detect the melanoma's intrinsic blood vessels, additional to the choroidal circulation, but is rarely needed for diagnosis unless to differentiate for alternative diagnostic options such as a choroidal hemangioma [2, 35]. This diagnostic method is however only able to demonstrate the superficial fluorescence and thus only a viable option in flat tumors [36]. In other cases, indocyanine green angiography is a better option for depicting the intrinsic vessels and may help to predict growth of small melanocytic tumors [37, 38].

Additional non-invasive procedures like fundus autofluorescence and optical coherence tomography are notably useful in diagnosing and monitoring small choroidal melanomas, which are particularly difficult to differentiate from benign nevi, as will be further described in the following paragraph. The SD-OCT with enhanced depth imaging may help in these cases by displaying already very little amounts of subretinal fluid, especially when over central tumors and signs such as shaggy photoreceptors are indicative for choroidal melanoma [35, 39]. The intrinsic and characteristic autofluorescence of small pigmented tumors is shown using fundus autofluorescence imaging, with bright hyperautofluorescence of orange pigment and subretinal fluid being also more often associated with melanoma [40, 41].

Further imaging methods, like magnetic resonance imaging (MRI) and computed tomography (CT) of the head, are rather not required neither for diagnosis nor tumor size classification, since ultrasonography is generally sufficient for this purpose. In some special cases, visualization of the fundus may be very difficult or even impossible due to e.g. substantial cataract, vitreous hemorrhage or retinal detachment and MRI or CT may help in this case. Apart from that, these imaging techniques will only find application when planning radiation therapy later in the therapeutic process [2, 35].

Finally, if the clinical picture is still uncertain, suspicion of a malignant process may be confirmed via biopsy and subsequent histology, immunohistology and/or cytogenetics. As an invasive procedure though, it is always associated with a risk of certain complications, which has to be taken into account. Nevertheless, trends move towards more frequent and earlier biopsy, either transretinal within a vitrectomy using special forceps, or via transretinal or transscleral fine needle aspiration without vitrectomy [2, 35]. This is not only happening with the aim of earlier treatment and improving prognosis but also to better determine the patient's prognosis first. Tumor biopsy allows genetic testing, both cytogenetic and molecular genetics. Via

techniques such as fluorescence in situ hybridization, comparative genomic hybridization and multiplex ligation-dependent probe amplification for very small tumor fragments, characteristic chromosomal abnormalities and imbalances that are highly associated with a poor prognosis can be detected, including chromosome 3 loss, 1p loss and 8q gain as described further above [42, 43]. Analysis of mRNA enables categorization of choroidal melanoma by their gene expression profiles into class 1 or class 2, with the latter being associated with a higher metastasis rate [44]. Further mutations correlated with high mortality include BAP-1 (breast cancer-associated protein 1) gene inactivation. Though identification of and research on these gene, protein and chromosome alterations is the basis for improved target-based therapies, genetic testing does not lead to therapeutic consequences so far but enhanced prognostication only [42, 45].

1.5 Differential diagnosis

Diagnosis of large or medium-sized choroidal melanomas with the use of ultrasonography and other available imaging methods, as described above, is rather unproblematic for the experienced ophthalmologist or ocular oncologist. In the Collaborative Ocular Melanoma Study clinicians correctly identified 99.7% of the tumors as choroidal melanomas [46]. In this size range challenges are the early discovery rather than the correct identification of the melanoma [30]. What poses more difficulties for the diagnostician is to differentiate small uveal melanomas from benign nevi and to filter out those nevi, which have the potential to grow and transform into a malignant entity. For some time the consensus was to monitor the nevus and wait for evidence of growth before treating it as a choroidal melanoma [47-49]. As recent studies on tumor doubling times however show, this may be too late concerning metastatic-free survival. At initial diagnosis of a choroidal melanoma, models suggest micrometastasis may have already started and to prevent this process, melanomas need to be diagnosed when still very small in size [29]. Therefore, general ophthalmologists are often enough confronted with the question of how to deal with what looks like a benign nevus but might already be a small choroidal melanoma. Uveal nevi may be found in as many as 5-10% of the Caucasian population and are therefore a lot more common than uveal melanomas, approximately only 1 of 500 will turn into a melanoma in the course of an adult lifetime [25, 35]. To identify those presumed nevi which have a higher risk of growth and transformation than average or which in fact already are malignant, key features have been researched as mentioned above and are by now well established in predicting this development. Shields et al. declared the following five risk characteristics, ophthalmologists should look for when evaluating a nevus or a small melanocytic tumor of unknown dignity:

tumor *thickness* over 2mm, subretinal *fluid*, *symptoms*, *orange pigment* and tumor *margin* within 3mm from the optic disc, briefly summarized in the mnemonic “to find small ocular melanoma”. If two of these five features were present, tumor growth could be observed in half of the patients. *Ultrasound hollowness*, the absence of a *halo* around the tumor and of *drusen* over the tumor are characteristics that were later added to those features by the same authors, complementing the mnemonic with “using helpful hints daily” [34, 50, 51]. About 95% of the apparent nevi that turned out to be or develop into a melanoma initially presented themselves with one or more of the five original risk features [33]. Suggested practical implications are the referral to an ocular oncologist in the presence of at least one high-risk characteristic and intermittent review otherwise [35].

Other differential diagnoses include the choroidal hemangioma, which are well distinguishable from melanoma due to the very characteristic behavior in the angiography as well as ultrasonography where the A-scan ultrasound image will show a highly reflective echo and in the B-scan the typical presentation is a solid “dome-shaped” lesion with soft contours [52].

Metastases in the choroid may present themselves with symptoms similar to those of the choroidal melanoma and are the most common malignant tumor manifestation of the eye. Clinically they can be difficult to differentiate from amelanotic melanomas but show in EDI-OCT the pathognomonic “lumpy-bumpy” surface of the retinal pigment epithelium. In 83% of the cases an underlying tumor disease is known, otherwise at least the lungs and mammae or prostate respectively should be controlled for the primary tumor within the scope of an interdisciplinary tumor search, since 70-85% of choroidal metastasis originate from there [53-55]. Ultimately, a tumor biopsy and subsequent histology will shorten the searching process elegantly but sometimes compromises visual acuity if centrally located and should therefore be indicated cautiously [35].

Further diagnoses, which involve the retina and are therefore possible to differentiate, are melanocytoma, congenital hypertrophy of the retinal pigment epithelium and other hamartoma. Moreover, pigment epithelial or retinal detachments either idiopathic or due to a peripheral exudative hemorrhagic chorioretinopathy can result in tumor-like lesions, so do macular bleedings in the scope of an age-related macular degeneration, which are for that reason called pseudotumor maculae [56].

1.6 Classification

The classification of choroidal and ciliary body melanoma in the current seventh edition of the TNM classification released by the American Joint Committee of Cancer is for the first time based on a large clinical database. An appointed task force of ophthalmic oncologist reviewed published evidence covering 7369 patients and established tumor stages representative for the accompanying survival probability. Staging of the T category is based on the anatomic size of the uveal melanoma quantified by tumor thickness and largest basal diameter, each combination corresponding to small (T1), medium-sized (T2), large (T3) or very large (T4) melanoma. For further subcategories, the existence of ciliary body or extraocular extension is taken into account. In combination with the node (N) and metastasis (M) category this results in six stage categories I, IIA-B, IIIA-C and a seventh category IV for systemic metastasis. 5-year survival probabilities span as wide as 96% in stage I to 3% in stage IV. [57, 58]

1.7 Therapy of choroidal melanoma

There are several options available for the treatment of choroidal melanomas and all of them are carried out with a curative approach. The tumor size and location play a crucial role for the choice of therapy and its result, which is primarily defined through the local control of the tumor, even in patients with known metastases. If a globe preserving treatment is chosen further criteria of interest that are influenced by the tumor and the applied therapy, are functional parameters like the patient's visual acuity and field. Apart from the tumor size, radio physical properties of the therapy and its complication rates, other factors that may have an impact on the choice of the treatment are patient characteristics like age, comorbidities, life expectancy and also his or her priorities, as well as the length and costs of the treatment plus possible subsequent treatments. [2] While during the 1970s the enucleation of the eye was the single most applied treatment of uveal melanomas, the trend towards more frequent eye saving therapies began in the 1980s and during 2006-2008 with almost two thirds, radiotherapies were the first line treatment in the USA, leaving only 28.3% of patients treated with surgery including enucleation [1]. This shift was not least due to evidence published by the Collaborative Ocular Melanoma Study (COMS) confirming equal survival rates also in longer follow-up of patients with medium-sized tumors independent of the choice of treatment, iodine plaque radiotherapy or enucleation, and the stimulated establishment of standardized plaques for episcleral brachytherapy thereafter [59].

There is however no standardized treatment for the choroidal melanoma and depending on the available options at the center where they are managed, patients with similar melanomas

regarding size and location, may receive different treatments. In very large tumors or if visual outcome is presumably poor, enucleation can still be a reasonable option to achieve local tumor control, as the primary goal, and will be performed under general anesthesia using an orbital implant [2, 60]. Other present available primary treatment possibilities are the following:

- external beam radiotherapy (including proton beam therapy or stereotactic radiation with photons)
- brachytherapy (e.g. $^{106}Ru/^{106}Rh$, ^{125}I)

Apart from that, the following therapies are common options for an adjuvant treatment in combination with radiation therapy or enucleation:

- laser therapy (e.g. transpupillary thermotherapy)
- surgical intraocular methods: transscleral or transretinal (endo-) resection [2, 61]

1.7.1 Brachytherapy

Ophthalmic brachytherapy was already introduced in the 1960s firstly with the use of ^{60}Co and has over the last three decades become a commonly used now well established eye-sparing treatment option of the choroidal melanoma [62, 63]. Under preferably general anesthesia, the melanoma is located and the radioactive plaque is sewn to the episcleral surface, to cover the tumor's base plus a safety margin of 2mm to include possible microscopic tumor extension. In the USA, the widely used radioactive agent is ^{125}I and the eye plaque promoted by the COMS consists of a bowl-shaped gold disc to block radiation into the orbit and a silicone insert with slots individually loadable with ^{125}I emitting seeds. In Europe, ^{106}Ru is the main radionuclide of choice, firstly introduced by Lommatzsch in the 1960s. The shielding metal used in these applicators is silver. With the radioactive material already integrated as a layer in between, an assembly is not needed and the whole applicator is notably thin. Both ^{125}I and ^{106}Ru applicators come in several diameters and forms, with the possibility of notched geometries in case of the tumor's proximity to the optic nerve [60, 64, 65]. After suturing the plaque onto the sclera, it will remain in place for several days depending on its dose rate and the tumor size, during this period radiation will be continuously delivered [2, 60]. ^{125}I decays via electron capture emitting gamma radiation with a halftime of 60 days, which makes it convenient for storage. Another advantage is the low photon energy which is mostly absorbed within the tumor, requiring less shielding material and sparing the anterior segment of 90% of the apex dose, which is 85 Gy [66, 67]. The beta emitter ^{106}Ru has an even steeper dose fall-off and thus less range, which makes this isotope

most useful in treating smaller melanomas, also because it may otherwise give very high doses to the sclera and retina. It has a halftime of 374 days, by far longer than the halftime of ^{125}I, and decays into the daughter nuclide ^{106}Rh, whose subsequent decay is the actual source of the therapeutic dose [64].

1.7.2 Proton beam therapy

Proton beam irradiation for the treatment of choroidal melanomas needs a very expensive cyclotron with high energy levels of at least 55 MeV and is thus a viable treatment option reserved only to a few centers worldwide, mostly in cooperation with a nuclear research center [68]. In Germany, proton beam therapy for eye tumors was firstly performed by the Department of Ophthalmology of the Charité – Universitätsmedizin Berlin in collaboration with the Helmholtz-Center Berlin starting in June 1998, with more than 2500 patients having received radiation since. Prior to radiation, surgery is needed for suturing four tantalum clips to the episclera, landmarking the tumor margins. These radiopaque markers allow the radiographical location of the tumor and planning of the treatment volume together with the use of MRI (in large tumors > 6mm), CT, ultrasound images and photographs of the tumor and ocular fundus, as well as the control and adjustment of the correct eye positioning during radiation treatment. The patient's head position is fixated with the help of an individually tailored mask, eyelids are carefully retracted and a LED light is indicating the necessary line of vision. Preparation, positioning and control of position need 20-30 minutes, whereas the actual radiation treatment itself only takes approximately 1 minute, generally taking place on 4 days with a fractionated dose of 15 CGE each session, reaching a total target volume dose of 60 CGE. 1 CGE equals 1.1 Gy due to the higher relative biological effectiveness of proton beam radiation. [2, 60, 69, 70]

Protons are heavy charged particles that can be accelerated by very powerful electric fields and then directed transconjunctival onto the uveal tumor. The dose deposition profile has a very characteristic depth path, with a steep rise of energy absorption to the tissue until a maximum and a following abrupt even steeper dosage drop (Bragg-peak). The radiation dose applied to the tumor tissue only reaches its maximum at the very end of its travel path, allowing an exact irradiation even of very small target volumes. The tissue depth, at which the maximum dose is received depends on the proton energy. In order to realize penetration into the tumor tissue as deep as 35 mm, the protons' kinetic energy should be 60-72 MeV. The sharp dose profile can be modified technically via range modulators to reach several Bragg-peaks and by doing so ensure an adequate uniform radiation of the entire target volume. The cylindrical travel path of the

proton beam and its very high energy sharpness create extremely steep dosage drops both lateral and distal, keeping any occurring scattered radiation to a minimum. Risk structures such as fovea and optic nerve can therefore be spared best possible. Posterior segment complications including radiation retinopathy and optic neuropathy however do occur, representing a serious impairment of the patient's visual outcome. Nevertheless, since the proton beam enters the patient's eye through the conjunctiva, anterior segment complications such as radiogenic cataract, sicca symptoms or secondary glaucoma are most common [2, 60, 69, 70].

1.7.3 Stereotactic therapy

Stereotactic irradiation is a younger teletherapy technique in treating choroidal melanomas, using photon beams which are directed at the tumor with the use of linear accelerators (LINAC) [71]. Therapy costs are less than the costs for proton beam radiotherapy [72, 73]. The generated dose profiles are much flatter than the ones of proton beams, therefore the irradiated target volume covers almost the entire eye at least in low dose ranges, and can even extent extraocular. Thus, dose deposition to healthy risk structures is potentially higher [74]. Advantageous is the lack of need for radiopaque markers and hence surgery prior to radiation. Treatment planning, which involves localizing and defining the tumor and target volume is based solely on CT and MRI or both, via image fusion, and subsequently dose deposition profiles for any possible angle of irradiation can be calculated and selected best possible, even through the entire head if necessary. Generally treatment uses multiple fractions and is referred to as fractionated stereotactic radiotherapy (SRT) [71]. In this case, irradiation is usually divided into 4-5 fractions in 7 days with a total dose of 50 to 70 Gy applied on the 80% isodose. Data on survival and tumor control rates are limited but have been reported to be equally good as the rates of proton beam irradiation [75]. Alternatively, photon beam radiation can be executed in one session using a very large single dose and is then referred to as stereotactic radiosurgery (SRS). Treatment planning is the same but instead of a linear accelerator as the source of the photon radiation beams, SRS utilizes a gamma knife invented by the neurosurgeon Lars Leksell in the 1960s, or a CyberKnife® introduced in the 1990s by Prof. John R. Adler [76]. To this point the applied single fraction dose has been reduced to 35-40 Gy (50% isodose) without compromising the therapeutic outcome [71]. Both SRT and SRS require ocular immobilization, which may be realized by a range of techniques, from retrobulbar anesthesia to vacuum suction cups for the gamma knife or computer-assisted eye tracking and automatic gating in LINACs [71]. It remains

to be seen what therapeutic outcome may be achieved in long-term follow-up studies, with concern of survival rates as well as the main risk structures fovea, optic nerve and ciliary body.

1.7.4 Transpupillary thermotherapy

The technique of transpupillary thermotherapy (TTT) was developed by Oosterhuis et al. in 1995 as a useful complementary treatment to radiation therapy for uveal melanomas [77]. During this procedure using a contact lens, a near-infrared diode laser (810nm) of 2-3mm diameter is directed through the fully dilated pupil and onto the tumor, exposing it to the laser beam for approximately 1 minute. This will induce local hyperthermia of temperatures from 45°C to 60°C resulting in tumor necrosis down to a tissue depth of 3.9mm. Treatment is performed under retrobulbar anesthesia, as it would be painful otherwise except in yet irradiated tumors [77, 78]. Because of high observed tumor recurrence rates in comparison to radiation therapy, TTT as a primary or even sole treatment is considered to be ineffective and should therefore be only performed as an adjuvant option [79].

1.7.5 Surgical therapy

Surgical tumor resection via endoresection or transscleral resection is regarded to only be a viable option in combination with radiation therapy, due to a fear of iatrogenic tumor seeding and an associated 10% resp. 30% local recurrence risk, if endoresection or transscleral resection respectively was performed solely [2, 80]. Endoresection is a possible treatment following radiation therapy, in cases where the irradiated tumor became ischemic and exudative which may lead to serous retinal detachment, uveitis, rubeosis iridis and neovascular glaucoma. The term and procedure of “Endoresection” was coined and described by Damato already in 1998. After total vitrectomy, the tumor including a small safety margin is cut out through a small retinotomy. Flattening of the retina is achieved by fluid-PFCL exchange following endolaser photocoagulation to destroy any residual tumor and attain retinopexy [81]. Earlier performed fluid-air exchange should be avoided due to the risk of pulmonary embolisms [82]. Finally, the eye is filled with silicone oil, which can be removed 12 weeks later. Complications that may occur are mainly owed to the vitrectomy procedure and include entry site tears, postoperative after-bleedings, subretinal bleedings, cataract and in the later course proliferative vitreoretinopathy (PVR) and transient acute glaucoma [80, 81].

Transscleral resection, also referred to as exoresection is a procedure that allows resection of very anteriorly located tumors. After preparation of a lamellar scleral flap, the tumor is excised

together with the inner sclera. Surgery takes place under controlled arterial hypotension, with a mean blood pressure of 40 mmHg to prevent expulsive hemorrhage. Postoperative bleedings occurring nevertheless, may call for a necessary early revision with total vitrectomy and endotamponade [2].

1.8 Complications after radiation therapy

Any treatment will inevitably result in retinal damage and retinal pigment epithelium damage, whether it is through mechanical or physical influence. This work focuses on the development of radiation retinopathy and optic neuropathy following proton beam radiotherapy. Other common complications, that were already mentioned above but are not discussed any further, include instabilities of the tear film with sicca symptoms and epiphora, conjunctival keratinization, extensive tumor exudations with the risk of subsequent macular edema, retinal detachment, rubeosis iridis and neovascular glaucoma, as well as PVR and bleedings in the scope of a surgical intervention. [60, 83-85]

1.8.1 Radiation retinopathy

Epidemiology

Radiation retinopathy including radiation maculopathy is a common complication that can occur after irradiation of ocular tumors as well as other sites of the head and usually results in a significant irreversible impairment of visual function [86, 87]. Stallard firstly described radiation retinopathy in 1933, in a patient with retinoblastoma treated with radon seeds [88]. In the last years the increased use of radiation as treatment for malignant diseases has raised the incidence of this complication. Exact rates of radiation retinopathy are not identified, but after radiation therapy of choroidal melanomas it is likely to appear in more than 50% of the cases – at least locally and temporally – due to the very high applied radiation dose. Radiation retinopathy is developing more often after radiation of posterior located tumors close to the fovea. This might be due to different sensitivities of the peripheral versus central retina to radiation damage [89, 90]. Development of radiation retinopathy can take months to several years after radiation. The median latency until first symptomatic manifestation is 2.6 years [2, 88, 91]. It has been reported that a total radiation dose of less than 35 Gy is relatively safe regarding development of retinopathy and optic neuropathy. However, exceptions exist and therefore no general threshold value can be determined, not least since individual factors like DNA repair capacity,

fractionation and dose rate play an important influential role [92-94]. Factors associated with a higher risk of radiation retinopathy development and its severity, are diabetes, hypertension, collagenosis, acute leukemia, certain chemotherapeutics and pregnancy. Diabetic retinopathy aggravates radiation-induced retinopathy [95-97].

Pathogenesis

Ionizing radiation leads to damages of cell membranes, organelles and DNA, either directly by disrupting chemical bonds or indirectly via production of free radicals. The resulting single- or double-strand breaks of the DNA may at first still be repaired, but as soon as the damage exceeds the cell's repair capacities, it will lose its ability to proliferate, eventually inducing cell death. When treating malignant tumors, to reach tumor control this is the intended effect on the tumor cells. However, it is inevitable that also healthy tissues take collateral damage, with rapidly dividing tissues being particularly sensitive to any DNA damage. With regards to radiation of the retina, it is the vascular endothelial cells being the most proliferative and hence most sensitive cells. Neurons, in comparison, do not divide anymore and are therefore more radio-resistant [84, 88]. When the endothelial cells take damage, they can at first still be replaced via increased mitosis and migration of neighboring cells. With a growing number of damaged cells, soon these repair mechanisms are depleted and the vascular wall will lose its integrity. The described underlying pathomechanism characterizes radiation retinopathy as a slowly progressive, occlusive vasculopathy. This is in analogy to diabetic retinopathy, with the difference however that in the latter form, it is the pericytes rather than the endothelial cells that become damaged the most. The loss of endothelial cells can be found mainly in the smaller retinal vessels, larger retinal and choroidal vessels may also be affected [98-100].

The consequence of this endothelial damage is an increase of permeability and coagulation activity with subsequent vascular occlusions and alteration of the microcirculation. Early manifestations are microaneurysms, telangiectasia and retinal edema or exudation from insufficient capillary beds. Narrower capillary lumen and local capillary closure cause ischemia and infarction. The hypoxic insult due to the vascular occlusion leads to disruption also of neuronal structures via apoptosis, necrosis and glial scarring. As retinopathy proceeds, nerve fiber layer infarctions can be seen in areas with confluent capillary defects and loss, and where focal retinal ischemia reduces axoplasmic transport cotton wool spots will present clinically [84, 88]. Hence, in retinopathy due to radiation a combination of both microvascular and neuronal damage is present, the two forms being mutually dependent. Acute and chronic capillary defects are initially being compensated through formation of collaterals and shunts but in the long run

progressive neuronal cell damage is inevitable. This in turn is accompanied by a changed neuronal metabolism and an accumulation of growth factors such as VEGF and as a result from the retinal ischemia, neovascularization develops, holding the risk of vitreous hemorrhages. In the latter stage, radiation retinopathy has become proliferative [101-103]. Similar to diabetic retinopathy there is also proof of an inflammatory aspect involved in the pathophysiology of radiation retinopathy, with an increased activation and invasion of microglia cells and macrophages in the retinal tissue after radiation [88].

Clinical signs

The clinical picture of radiation retinopathy as well as the angiographic behavior is reported to be identical to diabetic retinopathy [97]. Clinical signs include cotton wool spots, retinal hemorrhage, vascular occlusion, lipid exudates and microaneurysms. If any of these occur within 3 mm of the fovea or if a macular edema is present, – possibly only detectable via OCT –, this is referred to as radiation maculopathy, a subgroup of retinopathy [90, 104].

In 2005, Finger and Kurli created a classification of radiation retinopathy, the Finger classification as presented in table 1, to allow for a commonly acknowledged definition and grading of radiation retinopathy as well as a first prognosis of the associated visual outcome. According to this classification, the above stated findings, best spotted via ophthalmoscopy, define stage 1 retinopathy when located exclusively outside the macula or stage 2 when pathological findings are found in the macula. These stages are associated with a mild or moderate risk of visual impairment, respectively. When retinopathy has either become proliferative or macula edema has occurred and thus stage 3 is reached, visual loss has most likely already occurred and there is a severe risk of further impairment. Stage 4 radiation retinopathy is defined by additional vitreous hemorrhages or large ischemic retinal areas and visual prognosis is worst as is the probability of globe salvage [105].

Table 1: The Finger classification of radiation retinopathy (2005)

Stage	Sign	Symptom	Location	Best viewed by	Risk of vision loss
1	Cotton wool spots	None	Extramacular	Ophthalmoscopy	Mild
	Retinal hemorrhages	None	Extramacular	Ophthalmoscopy	Mild
	Retinal micro-aneurysms	None	Extramacular	Ophthalmoscopy	Mild
	Exudate	None	Extramacular	Ophthalmoscopy	Mild
	Retinal ischemia (< 5 disc areas)	None	Extramacular	Angiography	Mild
2	Above findings	None	Macular	Both	Moderate
3	Any combination of the above plus Retinal neovascularization Macular edema – new onset	Vision loss	 Extramacular Macular	Angiography	Severe
4	Any combination of the above plus Vitreous hemorrhage Retinal ischemia (≥ 5 disc areas)	Vision loss	 Vitreous Extramacular and macular	 Ophthalmoscopy Angiography	Severe

Therapeutic options

In the scope of a radiation-induced retinopathy, maculopathy and especially macular edema plays the major role regarding the impairment of the patient's visual function [106]. It is therefore not only in the focus of research on how to implement radiation therapy to better avoid the development of maculopathy, but also the aim of the available most commonly used therapeutic options of radiation retinopathy, which are currently represented by panretinal photocoagulation (PRP) treatment and intravitreal injections (IVI) of antibodies to vascular endothelial growth factor (VEGF) or the glucocorticoid triamcinolone acetonide. Panretinal

photocoagulation is performed in proliferative radiation retinopathy to reduce or prevent neovascularization and the associated often persistent vitreous hemorrhages, and has been shown to in fact successfully decrease this vascular proliferation. However, PRP has only moderate positive effects on the visual acuity directly after treatment, but in the long term is not able to stall visual loss [107-109]. Intravitreal injections of anti-VEGF such as bevacizumab (Avastin®; Genentech, San Francisco, USA) or ranibizumab (Lucentis®; Novartis, Basel, Switzerland) are used to also prevent neovascularization and reduce vascular permeability and thus the macular edema. Several uncontrolled studies could show a decrease of macular edema and an associated improvement or stabilization of visual acuity for some patients and for some time after injection of anti-VEGFs bevacizumab or ranibizumab as well as triamcinolone acetonide [110-115]. However, long-term visual improvement still is too seldom and patients' responses to the different agents and injection regimes vary too much to be able to accept any form of IVI treatment as standard therapy for radiation retinopathy let alone optic neuropathy. A standard protocol for the treatment of radiation retinopathy and maculopathy is not established yet, not least for a lack of prospective controlled studies investigating both treatment options. Recent therapy efforts and investigations have been directed towards the prevention of radiation-induced retinopathy prior to its manifestation, either using scatter laser or intravitreal bevacizumab injections. First results seem promising but still it remains to be seen if more authors can support the use of early interventions for the prevention of radiation retinopathy [116].

1.8.2 Radiation optic neuropathy

Irradiation of the posterior eye pole may induce yet another posterior segment complication that is radiation optic neuropathy. The underlying pathogenesis is equal to radiation retinopathy. In this case however, it is the endothelium of the peri- and intrapapillary vessels being affected by radiation. Latency until manifestation can be likewise long (over 1 year). In acute states, papillary edema and hemorrhages can present themselves in variable severity. This stage might be followed by a decrease in disease activity. Possible late complications comprise papillary shunt vessels, neovascularization or optic atrophy, as well as retinal ischemia. At present there is no assured therapy available for the treatment of radiation optic neuropathy [2].

Since this complication is a considerable contributor to vision loss culminating in the patient's blindness, the focus here lies on identifying those radiation parameters whose modification can prevent development of optic neuropathy wherever possible [106].

2. Aim of the study

With radiation therapy becoming the predominantly chosen treatment of choroidal melanomas and equally high associated tumor control rates, emphasis now more and more lies on the improvement of the patients' functional outcome. Complications such as radiation retinopathy and optic neuropathy, frequently occurring after irradiation of the posterior eye segment, pose a serious threat of a crucial limitation in visual function. Up until now, no generally established standardized therapy protocol exists for the treatment of these complications. The best therapy always remains the prevention. Therefore, a major aim second to ensuring tumor control when treating melanoma patients with proton therapy should be to best possible avoid any development of radiation retinopathy or optic neuropathy by optimizing radiation planning on the basis of known risk factors or – if prevention is no viable option – to identify those high risk patients for better communication and discussion of their visual prognosis already prior to treatment.

The present study deals with the long-term follow-up of choroidal melanomas after proton beam irradiation, with the focus on the radiation complications in question. Besides identifying incidence rates, the main aim of this study is to detect risk factors related to tumor characteristics and radiation parameters, which have a significant impact on the appearance of these complications. These results hopefully will be helpful in irradiation planning especially for centrally located tumors by facilitating the sometimes upcoming single case decisions which sensitive structures need to be protected most and to what extent when visual impairment is to be prevented best possible.

3. Methods

3.1 Patients

This retrospective study, approved by the local ethics committee, involved 1085 consecutive patients with choroidal melanomas who received proton beam therapy as a primary treatment at the Helmholtz Center Berlin in cooperation with the Department of Ophthalmology of the Charité – Universitätsmedizin Berlin between June 1998 and December 2013. Exclusion criteria were a total proton dose below 60 cobalt gray equivalents (CGE) and re-irradiation, surgical resection of the melanoma or endodrainage vitrectomy following proton beam irradiation [117]. Furthermore, only those patients were included into the study whose follow-up took at least 12 months after therapy. The cutoff date for the last observation in the patients' follow-up was December 23, 2014.

3.2 Confirmation of diagnosis

Confirmation of diagnosis and therapeutic indication was mainly based on the clinical examination and ultrasonography images as described in paragraphs 1.4 and 1.5. In rare cases, where there was still uncertainty about the diagnosis, a tumor biopsy was performed for histopathological validation.

3.3 Implementation of the proton beam radiotherapy

The implementation of the proton beam radiation therapy and the pre-treatment process took place as already described in section 1.7.2.

3.4 Data collection and analysis

Data analysis was based on an existent data base of the Department of Ophthalmology of the Charité – Universitätsmedizin Berlin on choroidal melanoma patients treated with proton beam radiation. This existent data base covered demographic data, tumor characteristics, initial visual acuity and radiation parameters of the whole study population irradiated between June 1998 and December 2013. Furthermore, this data base contained follow-up data including last examination date, visual acuity and presentation of a posterior segment complication of the patients irradiated between June 1998 and December 2008, as listed in the following paragraphs. All of these patient data and ophthalmological findings relevant for treatment planning and prognosis,

including radiation parameters itself, had already been recorded prior to radiation as well as during medical follow-up and entered into this data base. No additional clinical examination was carried out afterwards. Concerning patients receiving treatment starting from January 2009 onwards, the following data was missing in the data base and therefore collected based on the review of electronic health records, operative reports and discharge letters: manifestation of a posterior segment complication and the date thereof, last follow-up and visual acuity on the last follow-up.

For analysis, those features were taken into account that potentially could have an impact on the development of posterior segment complications and visual outcome. The following data were evaluated.

3.4.1 Demographic data

To determine the demographic distribution the following data were gathered and analyzed for all patients:

- Age at therapy
- Gender
- Affected eye

3.4.2 Tumor characteristics

Prior to radiation treatment the key attributes of the patient's melanoma as displayed in table 2 were obtained, characterizing the tumor in terms of size, location and classification.

Table 2: Tumor characteristics

Tumor characteristics	
Continuous variables	
Prominence	in mm
Base diameter	in mm
Volume	in mm^3
Distance to fovea	in mm
Distance to optic disc	in mm
Distance to equator	in mm
Categorical variables	
Diagnosis	choroidal melanoma choroidal-ciliary body melanoma choroidal-ciliary body-iris melanoma
T-category	in gradings T1, T2, T3, T4
Location relative to fovea	close to fovea (distance to fovea ≤ 2.5 mm) far from fovea (distance to fovea > 2.5 mm)
Location relative to optic disc	close to optic disc (distance to optic disc ≤ 2.5 mm) far from optic disc (distance to optic disc > 2.5 mm)

3.4.3 Radiation parameters

On the basis of the patient's tumor characteristics an irradiation plan was calculated and then executed. The following parameters were obtained from these irradiation plans:

- total proton dose in CGE
- number of fractions
- average dose on fovea in CGE
- average dose on optic disc in CGE
- irradiated optic nerve length in mm
- irradiated ciliary body sector in clock hours

3.4.4 Visual acuity

The patient's visual acuity was measured and recorded in DIN values prior to radiation treatment. For the correct calculation and analysis of the average visual acuity, the geometric mean has to be used. Therefore, DIN values were converted in logMAR using table 3, based on Holladay (2004) [118]. Hereafter, visual acuity values are shown in logMAR.

Table 3: Conversion of the snellen vision equivalents into logMAR and DIN

Snellen equivalent (feet)	logMAR	Decimal equivalent (DIN resp. EN ISO)	MARAN (adjusted meter vision)
	2.2		No Light Perception
	2.1		Light Perception
	2.0		Hand Motion
	1.9		Counting Fingers
	1.8		
	1.7	0.02	
20/800	1.6	0.03	
	1.5		
20/500	1.4	0.04	
20/400	1.3	0.05	
20/320	1.2	0.06	
20/250	1.1	0.08	
20/200	1.0	0.10	
20/160	0.9	0.125	
20/125	0.8	0.16	
20/100	0.7	0.20	
20/80	0.6	0.25	
20/63	0.5	0.32	
20/50	0.4	0.40	
20/40	0.3	0.50	
20/32	0.2	0.63	
20/25	0.1	0.80	
20/20	0.0	1.00	
20/16	-0.1	1.25	

3.4.5 Follow-up

Based on the discharge letters and electronic health reports each patient's latest ophthalmological check-up was documented. The observation time was recorded in month. In addition, latest visual acuity test results were obtained.

3.4.6 Posterior segment complications

After irradiation of the eye typical posterior segment complications may occur. Discharge letters in the follow-up of the patients were reviewed for appearance of one of the complications listed below, which were then recorded with the time of their first diagnosis in month after irradiation.

3.4.6.1 Radiation retinopathy

We defined radiation retinopathy as a new onset of:

- Cotton wool spots
- Hemorrhages
- Micro-aneurysms
- Exudates
- Ischemia

concerning the retina and/or the macula.

Retinal ischemia was diagnosed by means of fluorescein angiography. Macular edema in the scope of a radiation retinopathy was in some cases determined using optical coherence tomography.

3.4.6.2 Radiation optic neuropathy

The diagnosis of radiation optic neuropathy was made when there were clinical signs of:

- Disc edema
- Hemorrhages at the optic nerve head
- Progressive pallor of the optic nerve head
- Optic atrophy

3.5 Statistical analysis

All examination results and findings were entered into a standardized software program. The collected data were entered numerically encoded into “Microsoft® Office Excel Program” and afterwards statistically evaluated using SPSS (Statistical Package for Social Sciences) for Windows Release 22.0.

Based on the Kaplan-Meier method survival estimates were generated, as were annual and cumulative proportions of patients presenting radiation retinopathy and optic neuropathy respectively. Patient survival was calculated from the first day of radiation therapy until initial diagnosis of a posterior segment complication stated above. All survival analyses were censored at the time of the last observation. Categorical variables were described by indication of absolute and relative frequencies. For continuous variables descriptive statistics included the specification of means, standard deviations, median, minimum and maximum (range). Between-group comparisons were performed with the use of the Pearson-chi-square test in case of nominally scaled data. The mean differences of metrically scaled data were generally verified with the Mann-Whitney-U-test, since these were mostly not normally distributed as checked for using the Kolmogorov-Smirnov-test. If the comparison covered more than two groups, the Kruskal-Wallis-test applied. The significance level was set at 0.05 for all statistical tests, which were performed using two-sided tests. Radiation dose as a predictor of radiation retinopathy and optic neuropathy was evaluated using Cox’s proportional hazards regression. Probabilities for each complication according to the doses applied to the fovea and the optic disc respectively were estimated using binary logistic regression and the relationship of these doses and the respective probability was analyzed with linear regression. To identify the explanatory variables for the appearance of radiation retinopathy and optic neuropathy, respectively, those variables, which the univariate analysis revealed to be significant, were entered into a multiple regression analysis. Except for the latter multivariate analysis, which was performed by an external medical statistician, all analyses were conducted by the author of this work.

4. Results

4.1 Patient characteristics

4.1.1 Demographic data

In total, 1085 patients were included into this study, 551 of them were men and 534 were women.

Table 4: Gender distribution

Gender	number	%
Male	551	50.8
Female	534	49.2
Total	1085	100

At the first day of proton beam therapy the mean patient's age was 60.7 years, with the youngest being 16 years old and the oldest patient being 89 years old.

Table 5: Patient age at the date of proton therapy

Patient age	Years
Mean	60.7
Standard deviation	13.4
Median	62.0
Minimum	16
Maximum	89

4.1.2 Diagnosis and treatment

By far the most frequent treatment diagnosis was the choroidal melanoma (95.4%). Only 50 patients suffered from choroidal-ciliary body melanoma, with the iris additionally being affected in 3 of them.

Table 6: Treatment diagnosis

Diagnosis	number	%
Choroidal melanoma	1035	95.4
Choroidal-ciliary body melanoma	50	4.6
Total number	1085	100

With regards to the site, 576 right eyes (53.1%) and 509 left eyes (46.9%) were irradiated with a mean total proton dose of 60 CGE. In 5 cases, the patients received a total proton dose of 65 CGE or more (maximum: 75 CGE). In 99.2% of the cases total radiation dose was divided into 4 fractions. Only one patient was irradiated in one session and in 8 patients total proton dose was partitioned into 5 or 8 fractions. Since almost the whole patient group was irradiated in 4 fractions and a total proton dose of 60 CGE, these variables were not taken into account in the later analysis of possible impact factors on the appearance of radiation complications, due to a lack of statistical significance and power.

Table 7: Distribution of total proton dose and fractions

		number	%
Total proton dose	60	1080	99.5
(in CGE)	65	2	0.2
	70	2	0.2
	75	1	0.1
Fractions	1	1	0.1
	4	1076	99.2
	5	3	0.3
	8	5	0.5
Total		1085	100

4.2 Follow-up

4.2.1 Observation period

The patients' mean observation time was 54.4 months ranging from 12 months (minimum inclusion criterion) to the longest observation period of 170.4 months.

Table 8: Observation period since proton therapy

Observation period	**months**
Mean	54.4
Standard deviation	34.6
Median	48.1
Minimum	12.0
Maximum	170.4

4.2.2 Manifestation of radiation retinopathy and optic neuropathy

Of the 1085 patients, 267 (24.6%) survived without the diagnosis of a radiation retinopathy or optic neuropathy during follow-up, leaving 818 patients (75.4%) being diagnosed a posterior segment complication of that kind. Mean complication-free survival was estimated 32.4 months based on the Kaplan-Meier method. After an estimated 21.6 months as of proton beam therapy, half of the patients have suffered a posterior segment complication in question.

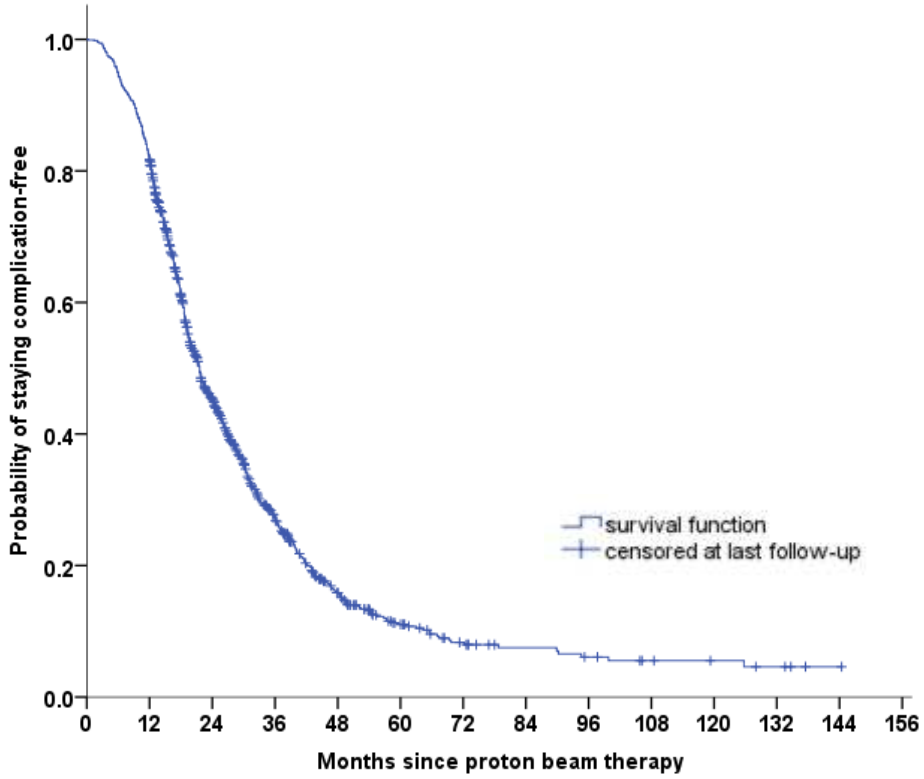

Figure 1: Kaplan-Meier analysis of complication-free survival

Table 9 shows the annual and cumulative rates of each posterior segment complication of interest, calculated on the basis of life table approaches. After 5 years since proton therapy (PT) 86.1% had shown signs of radiation retinopathy. The highest risk of developing a retinopathy was in the second year post-treatment, where as many as 40% received this diagnosis. In the following years rates declined, yet those who survived 5 years without any signs still only had a 50% chance of staying complication-free thereafter. Diagnosis of radiation optic neuropathy also peaked in the second year post-irradiation, but was overall more seldom with a little more than half of the patients presenting signs of optic neuropathy in the first 5 years after proton radiation.

Table 9: Annual and cumulative incidences of complications

Years since PT	No. at Risk	No. Events	Annual Rate	Cumulative Rate
Retinopathy				
0-1	1085	153	14.1%	14.1%
1-2	867	354	40.8%	49.2%
2-3	414	156	37.7%	68.3%
3-4	206	79	38.3%	80.5%
4-5	97	28	29.0%	86.1%
>5	38	20	53.3%	93.5%
Optic neuropathy				
0-1	1085	96	8.8%	8.8%
1-2	897	187	20.8%	27.9%
2-3	550	90	16.4%	39.7%
3-4	351	52	14.8%	48.6%
4-5	212	16	7.5%	52.5%
>5	91	31	34.3%	68.8%

Radiation retinopathy

In this study, 790 patients (72.8%) suffered from radiation retinopathy including maculopathy. Maculopathy was diagnosed in 224 patients, representing 28.4% of those with manifestation of a retinopathy. The patient group consisted of 383 men (48.5%) and 407 women (51.5%).

Table 10: Total number of radiation retinopathy

Radiation retinopathy	number	percent
Yes	790	72.8
No	295	27.2
Total	1085	100

Median observation time in this group was 55.8 months, ranging from 12.6 to 170.4 months. The mean observation time of 61.5 months differed significantly to the mean observation time of 35.3 months in the cohort of patients without the diagnosis of radiation retinopathy in the follow-up (two-sided significance $p<0.001$ in the Mann-Whitney-U-test).

Table 11: Observation period in the radiation retinopathy group

	Radiation retinopathy	
Observation period (months)	**Yes (n=790)**	**No (n=295)**
Mean	61.5	35.3***
Standard deviation	34.5	26.7
Median	55.8	26.6
Minimum	12.6	12.0
Maximum	170.4	167.4

Note: *** stands for the 1% (2-sided) significance level of the Mann-Whitney-U-test.

First appearance of radiation retinopathy was after a median of 18.9 months. At the earliest retinopathy appeared after only 1.4 months but no later than 99.8 months.

Table 12: Initial manifestation of radiation retinopathy

Initial manifestation	months
Mean	23.0
Standard deviation	14.4
Median	18.9
Minimum	1.4
Maximum	99.8

After an estimated 24.1 months using the Kaplan-Meier method, the patients' probability to survive without any manifestation of radiation retinopathy was 50%. Further retinopathy-free survival rates of interest were calculated to be 85.9% for one year, 50.2% for two years, 30.9% for three years, 18.7% for four years and 13.3% for five years since proton beam therapy.

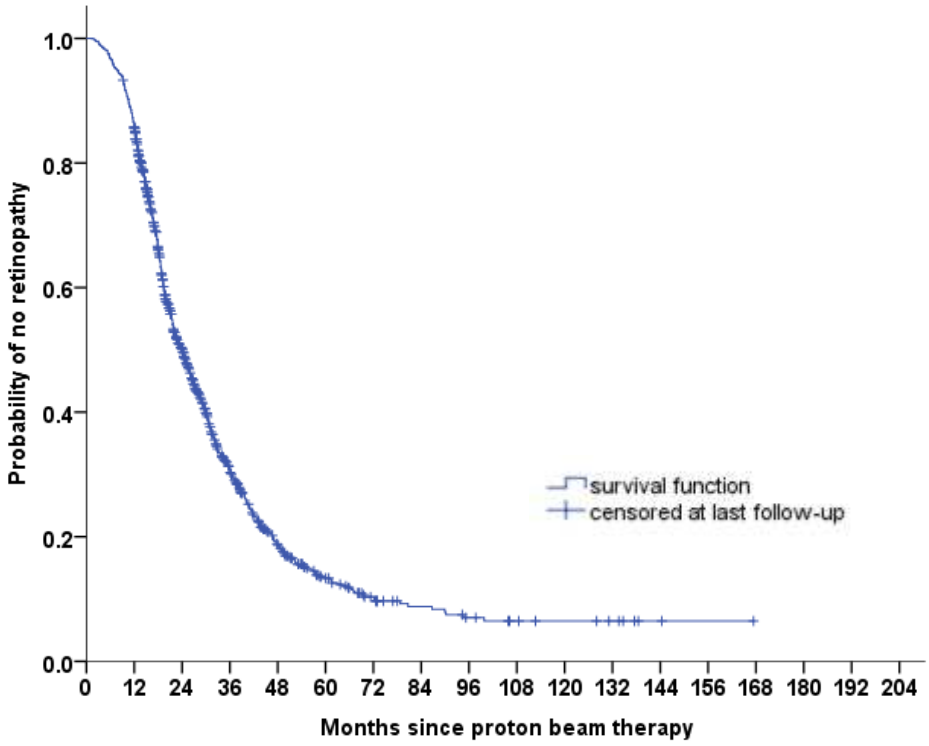

Figure 2: Kaplan-Meier analysis of survival without radiation retinopathy

Radiation optic neuropathy

In 472 patients (43.5%), radiation optic neuropathy occurred. This cohort comprised 232 (49.2%) male and 240 (50.8%) female patients.

Table 13: Total number of radiation optic neuropathy

Radiation optic neuropathy	number	percent
Yes	472	43.5
No	613	56.5
Total	1085	100

The median observation time in this group was 64.1 months and again significantly longer than in those patients without manifestation of radiation optic neuropathy (two-sided significance $p<0.001$ in the Mann-Whitney-U-test).

Table 14: Observation period in the radiation optic neuropathy group

	Radiation optic neuropathy	
Observation period (months)	**Yes (n=472)**	**No (n=613)**
Mean	69.4	42.8***
Standard deviation	35.9	28.6
Median	64.1	34.8
Minimum	12.4	12.0
Maximum	169.7	170.4

Note: *** stands for the 1% (2-sided) significance level of the Mann-Whitney-U-test.

Diagnosis was initially made after a median of 19.8 months, ranging from 0.2 months to 125.7 months since radiation therapy.

Table 15: Initial manifestation of radiation optic neuropathy

Initial manifestation	months
Mean	25.6
Standard deviation	19.4
Median	19.8
Minimum	0.2
Maximum	125.7

Based on Kaplan-Meier survival analysis, patients had a 50% chance of surviving without the diagnosis of radiation optic neuropathy for as long as 51.7 months after being irradiated. The probabilities to stay optic neuropathy-free for 1 year, 2 years, 3 years, 4 years and 5 years after proton beam therapy were estimated to be 91%, 72%, 60%, 51.1% and 47.2%, respectively.

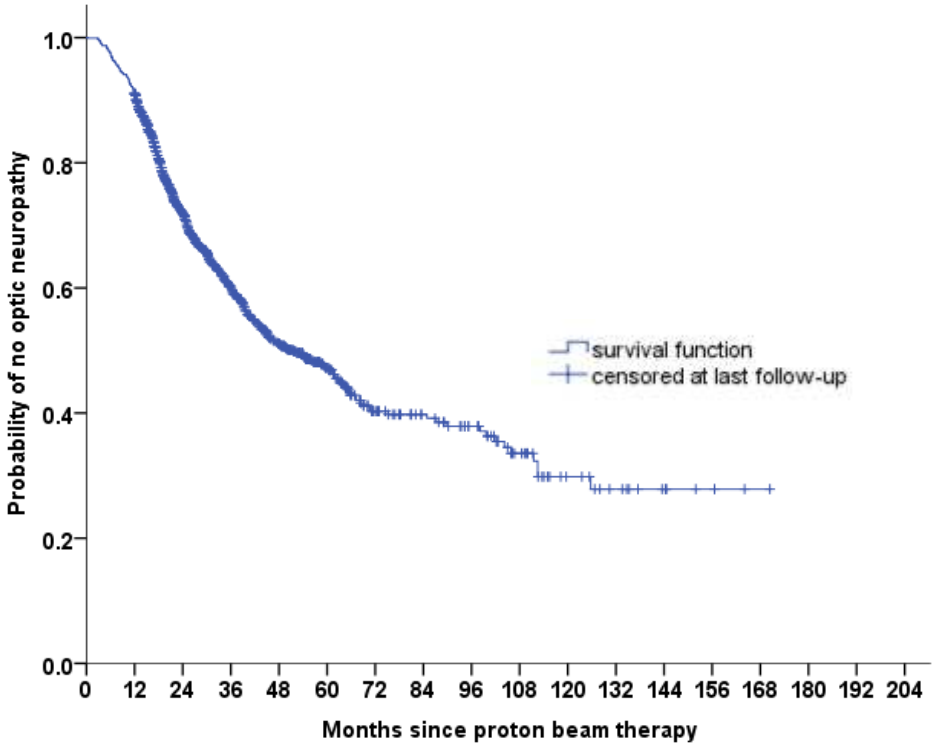

Figure 3: Kaplan-Meier analysis of survival without radiation optic neuropathy

In order to identify factors that have a significant impact on the occurrence of radiation retinopathy and radiation optic neuropathy, respectively, further analysis and evaluation of the aforementioned parameters such as tumor characteristics and radiation parameters, was carried out and will be hereafter presented on the basis of group comparisons. Firstly, both posterior segment complications are treated as one group, followed by a separate presentation of the patient cohorts with a diagnosed radiation retinopathy or radiation optic neuropathy, respectively.

4.3 Analysis of possible impact factors on the incidence of radiation retinopathy and optic neuropathy

4.3.1 Univariate analysis

4.3.1.1 Patient characteristics

Posterior segment complication versus no complication

The gender distribution in the patient cohort with diagnosed radiation retinopathy or optic neuropathy was significantly different to the cohort with no complication (two-sided significance p=0.030 in the Pearson-Chi-Square test).

Table 16: Crosstabulation of gender and posterior segment complication

		Radiation retinopathy or optic neuropathy		
		Yes	**No**	**Total**
Gender	**male**	400 (72.6%)	151 (27.4%)	534 (100%)
	female	418 (78.3%)	196 (21.7%)	625 (100%)
Total		845 (75.4%)	450 (24.6%)	1295 (100%)

Patients developing a radiation retinopathy or optic neuropathy during the observational period were significantly younger with a mean age of 59.9 years ± 13.2 years compared to a mean age of 63.2 years ± 14.0 years in the patient group without a diagnosed posterior segment complication.

Table 17: Patient age comparison between posterior segment complication and no complication

	Radiation retinopathy or optic neuropathy	
Patient age (years)	**Yes (n=818)**	**No (n=267)**
Mean	59.9	63.2***
Standard deviation	13.2	14.0
Median	61.0	66.0
Minimum	16	22
Maximum	88	89

Note: *** stands for the 1% (2-sided) significance level of the Mann-Whitney-U-test.

Similarly, the distribution of the treatment diagnosis varied significantly between these groups (two-sided significance p<0.001 in the Pearson-Chi-Square test), with choroidal-iris-ciliary body melanoma and choroidal-ciliary body melanoma being less associated with the development of a posterior segment complication than the choroidal melanoma, indicating a first possible impact of the tumor location relative to the posterior segment.

Table 18: Crosstabulation of treatment diagnosis and posterior segment complication

		Radiation retinopathy or optic neuropathy		
		Yes	**No**	**Total**
Treatment diagnosis	**Choroidal-ciliary body melanoma**	20 (2.4%)	30 (11.2%)	50 (4.6%)
	Choroidal melanoma	798 (97.6%)	237 (88.8%)	1035 (95.4%)
Total		818 (100%)	267 (100%)	1085 (100%)

Radiation retinopathy versus no radiation retinopathy

Looking at radiation retinopathy solely, in comparison to the patients without a diagnosed radiation retinopathy, gender and age distribution shows a similar picture. 76.2% of the female patients developed radiation retinopathy, whereas male patients developed this complication a little less often (69.5%) (two-sided significance p=0.013 in the Pearson-Chi-Square test).

Table 19: Crosstabulation of gender and radiation retinopathy

		Radiation retinopathy		
		Yes	**No**	**Total**
Gender	**male**	383 (69.5%)	168 (30.5%)	551 (100%)
	female	407 (76.2%)	127 (23.8%)	534 (100%)
Total		790 (72.8%)	295 (27.2%)	1085 (100%)

Mean age of the patients with diagnosed radiation retinopathy was 59.7 years and thus significantly although not much younger than the mean age of 63.3 of the patients in the group without a radiation retinopathy appearing in the follow-up period.

Table 20: Patient age comparison between radiation retinopathy and no radiation retinopathy

	Radiation retinopathy	
Patient age (years)	**Yes (n=790)**	**No (n=295)**
Mean	59.7	63.3***
Standard deviation	13.1	14.1
Median	61.0	66.0
Minimum	16	22
Maximum	88	89

Note: *** stands for the 1% (2-sided) significance level of the Mann-Whitney-U-test.

Choroidal melanoma was again significantly more often the treatment diagnosis in the group of radiation retinopathy patients. 97.5% compared to 89.8% of the other group were irradiated because of this diagnosis (two-sided significance $p<0.001$ in the Pearson-Chi-Square test).

Table 21: Crosstabulation of treatment diagnosis and radiation retinopathy

		Radiation retinopathy		
		Yes	**No**	**Total**
Treatment diagnosis	**Choroidal-ciliary body melanoma**	20 (2.5%)	30 (10.2%)	50 (4.6%)
	Choroidal melanoma	770 (97.5%)	265 (89.8%)	1035 (95.4 %)
Total		790 (100%)	295 (100%)	1085 (100%)

Radiation optic neuropathy versus no radiation optic neuropathy

Gender distribution did not vary significantly between the two groups of concern. In the study, 42.1% of all men and 44.9% of all women developed a radiation optic neuropathy after proton beam therapy (two-sided significance p=0.346 in the Pearson-Chi-Square test).

Table 22: Crosstabulation of gender and radiation optic neuropathy

		Radiation optic neuropathy		
		Yes	**No**	**Total**
Gender	**male**	232 (42.1%)	319 (57.9%)	551 (100%)
	female	240 (44.9%)	294 (55.1%)	534 (100%)
Total		472 (43.5%)	613 (56.5%)	1085 (100%)

The mean patient in the population with later manifestation of radiation optic neuropathy was 59.8 years old and thus only slightly but still significantly younger than the mean patient without diagnosed radiation optic neuropathy whose age was 61.4 years (two-sided significance p=0.023 in the Mann-Whitney-U-test).

Table 23: Patient age comparison between radiation optic neuropathy and no radiation optic neuropathy

	Radiation optic neuropathy	
Patient age (years)	**Yes (n=472)**	**No (n=613)**
Mean	59.8	61.4**
Standard deviation	13.0	13.7
Median	62.0	63.0
Minimum	20	16
Maximum	88	89

Note: ** stands for the 5% (2-sided) significance level of the Mann-Whitney-U-test.

Except for 3 patients, all other patients (99.4%) with manifestation of radiation optic neuropathy had been diagnosed with choroidal melanoma. This percentage was significantly larger than the percentage in the comparison group, where only 92.3% were irradiated on a choroidal melanoma and 7.3% on a choroidal-ciliary body melanoma (two-sided significance p<0.001 in the Pearson-Chi-Square test).

Table 24: Crosstabulation of treatment diagnosis and radiation optic neuropathy

		Radiation optic neuropathy		
		Yes	**No**	**Total**
Treatment diagnosis	**Choroidal-ciliary body melanoma**	3 (0.6%)	47 (7.6%)	50 (4.6%)
	Choroidal melanoma	469 (99.4%)	566 (92.3%)	1035 (95.4%)
Total		472 (100%)	613 (100%)	1085 (100%)

4.3.1.2 Tumor characteristics

Tumor stage

Posterior segment complication versus no complication

There was a highly significant difference in the tumor stage distribution between the two groups of concern (two-sided significance p<0.001 in the Pearson-Chi-Square test). 85.4% of the patients with a diagnosed radiation retinopathy or optic neuropathy had a tumor of stage T1 or T2, as opposed to only 70.8% in the complication-free group.

Table 25: Crosstabulation of tumor stage and posterior segment complication

		Radiation retinopathy or optic neuropathy		
		Yes	**No**	**Total**
Tumor stage	**T1**	306 (37.4%)	98 (36.7%)	404 (37.2%)
	T2	393 (48.0%)	91 (34.1%)	484 (44.6%)
	T3	101 (12.3%)	61 (22.8%)	162 (14.9%)
	T4	18 (2.2%)	17 (6.4%)	35 (3.2%)
Total		818 (100%)	267 (100%)	1085 (100%)

Radiation retinopathy versus no radiation retinopathy

As shown in table 26, the distribution of the different tumor stages in patients who developed radiation retinopathy was almost identical. 85.6% of the patients' tumors in the radiation retinopathy group were staged T1 or T2 prior to radiation, in the patients without radiation retinopathy T1 and T2 tumors made up only 71.9% (two-sided significance $p<0.001$ in the Pearson-Chi-Square test).

Table 26: Crosstabulation of tumor stage and radiation retinopathy

		Radiation retinopathy		
		Yes	**No**	**Total**
Tumor stage	**T1**	294 (37.2%)	110 (37.3%)	404 (37.2%)
	T2	382 (48.4%)	102 (34.6%)	484 (44.6%)
	T3	96 (12.2%)	66 (22.4%)	162 (14.9%)
	T4	18 (2.3%)	17 (5.8%)	35 (3.2%)
Total		790 (100%)	295 (100%)	1085 (100%)

Radiation optic neuropathy versus no radiation optic neuropathy

The tumor stages in the group of radiation optic neuropathy patients and in the retinopathy group were equally distributed, and, similarly, distribution differed significantly from the tumor stage distribution in the cohort without radiation optic neuropathy (two-sided significance $p=0.001$ in the Pearson-Chi-Square test). Table 27 below shows an 85.8% prevalence of tumor stages T1 and T2 in the radiation optic neuropathy group versus 78.8% prevalence in the counter group.

Table 27: Crosstabulation of tumor stage and radiation optic neuropathy

		Radiation optic neuropathy		
		Yes	**No**	**Total**
Tumor stage	**T1**	174 (36.9%)	230 (37.5%)	404 (37.2%)
	T2	231 (48.9%)	253 (41.3%)	484 (44.6%)
	T3	61 (12.9%)	101 (16.5%)	162 (14.9%)
	T4	6 (1.3%)	29 (4.7%)	35 (3.2%)
Total		472 (100%)	613 (100%)	1085 (100%)

Tumor size and location

Posterior segment complication versus no complication

Of the three parameters of interest quantifying the tumor in size, diameter and volume differed significantly between the group of patients who suffered radiation retinopathy or optic neuropathy and of those who did not (two-sided significance $p<0.05$ in the Mann-Whitney U-test). The group without a diagnosed radiation retinopathy or optic neuropathy was irradiated on larger melanomas. Mean tumor diameter and volume differed significantly by 0.73 mm and 133.78 mm^3, respectively. Mean tumor prominence differed by 0.70 mm, but not significantly.

In terms of location, tumors in the patient group that developed a posterior segment complication were significantly closer to this eye segment and the more sensitive structures, optic disc and fovea. In the complication group, the mean tumor was located 3.3 mm posteriorly of the equator, whereas in patients without any such complication, it was situated 0.3 mm anteriorly of the equator (two-sided significance $p<0.001$ in the Mann-Whitney-U-test). Moreover, melanomas in this group were significantly more often found to be close to the fovea (80.8%) and the optic disc (68.9%) when compared with the cohort without a diagnosed manifestation of radiation retinopathy and/or optic neuropathy (62.5% and 42.7% respectively) (two-sided significance $p<0.001$ in the Pearson-Chi-Square-test). Mean differences between the two groups in the tumor's distance to the fovea and optic disc were calculated to be 1.39 mm and 1.87 mm, respectively, and verified to be significant with the Mann-Whitney-U-test (two-sided significance $p<0.001$). Results are presented in tables 28 and 29.

Radiation retinopathy versus no radiation retinopathy

Tables 30 and 31 show a confirmation of the former results also for the analysis limited to patients diagnosed with radiation retinopathy, with tumor characteristics values being almost the same as in the aggregated complication group, since 96.6% of this group is made up of patients with diagnosed radiation retinopathy. If there is anything to add to the findings concerning tumor size and location specifically for this group, it is that the tumors tended to be even closer to the fovea. 50% of all tumors in the radiation retinopathy group were attached to the fovea (distance to fovea 0.0 mm) and 80.8% were close to the fovea. All continuous and categorical variables were significantly different between the two groups on a level $p<0.05$ in the Mann-Whitney-U-test resp. Pearson-Chi-Square test, except for tumor prominence, which did not differ significantly.

Radiation optic neuropathy versus no radiation optic neuropathy

Results for the analysis of the tumor characteristics in the radiation optic neuropathy patient group were once more very similar to those of the radiation retinopathy analysis as shown in tables 32 and 33. Tumors in this group were smaller in size, indicated by prominence, diameter and volume, though not significantly. But again they were highly significantly closer to the posterior segment and the vulnerable structures fovea and optic disc than the tumors in the group of patients without a diagnosed radiation optic neuropathy (two-sided significance $p<0.001$ in the Mann-Whitney U-test), although mean differences of most variables were not as large as in the retinopathy group comparison except for the distance to the optic disc. In 472 patients where radiation optic neuropathy occurred during follow-up, 84.3% of the tumors were located close to the optic disc, leaving only 15.7% of the tumors far from the optic disc. This distribution was found to be significantly different to that in the patient cohort without radiation optic neuropathy, where only 45.7% of the patients' tumors were located close to the optic disc (two-sided significance $p<0.001$ in the Pearson-Chi-Square-test). With 50% of the tumors attached to the optic disc, the mean distance to the optic disc in the radiation optic neuropathy group was 1.0 mm, tumors thus being 2.4 mm from this structure, which is significantly closer than in the contrast group (two-sided significance $p<0.001$ in the Mann-Whitney-U-test).

Table 28: Tumor size and location comparison between posterior segment complication and no complication

	Radiation retinopathy/optic neuropathy						No radiation retinopathy/optic neuropathy					
Tumor characteristics	n	Mean	SD	Min	Median	Max	n	Mean	SD	Min	Median	Max
Size												
Prominence (mm)	818	3.9	1.8	0.0	3.6	14.1	267	4.6	2.7	0.7	3.7	14.0
Diameter (mm)	818	11.1	3.1	3.3	10.8	22.4	267	11.8**	3.7	3.0	11.4	21.8
Volume (mm^3)	818	258.4	281.5	0	175.5	2535	267	392.2**	472.7	3	210.0	2686
Location												
Distance to fovea (mm)	818	1.3	2.2	0.0	0.0	17.5	267	2.7***	3.6	0.0	1.5	18.5
Distance to optic disc (mm)	818	1.9	2.5	0.0	1.2	17.0	267	3.8***	3.6	0.0	3.0	18.3
Distance to equator (mm)	817	3.3	5.6	-17.3	4.8	14.3	267	-0.3***	6.5	-18.0	0.4	13.3

Note: *** stands for the 1% (2-sided) significance level of the Mann-Whitney-U-test.
** stands for the 5% (2-sided) significance level of the Mann-Whitney-U-test.

Table 29: Crosstabulation of tumor location and posterior segment complication

	Radiation retinopathy or optic neuropathy		
	Yes	**No**	**Total**
Location relative to fovea			
Close to fovea	661 (80.8%)	167 (62.5%)	828 (76.3%)
Far from fovea	157 (19.2%)	100 (37.5%)	257 (23.7%)
Location relative to optic disc			
Close to optic disc	564 (68.9%)	114 (42.7%)	678 (62.5%)
Far from optic disc	254 (31.1%)	153 (57.3%)	407 (37.5%)
Total	818 (100%)	267 (100%)	1085 (100%)

Table 30: Tumor size and location comparison between radiation retinopathy and no radiation retinopathy

	Radiation retinopathy					No radiation retinopathy					
Tumor characteristics	n	Mean	SD	Min	Median	Max	n	Mean	SD	Min	Median	Max
Size												
Prominence (mm)	790	3.9	1.8	0.0	3.6	14.1	295	4.5	2.7	0.7	3.7	14.0
Diameter (mm)	790	11.1	3.1	3.3	10.9	22.4	295	11.8**	3.6	3.0	11.4	21.8
Volume (mm^3)	790	259.1	284.1	0	175.5	2535	295	377.6**	455.9	3	210	2686
Location												
Distance to fovea (mm)	790	1.3	2.2	0.0	0.0	17.5	295	2.6***	3.5	0.0	1.5	18.5
Distance to optic disc (mm)	790	1.9	2.5	0.0	1.2	17.0	295	3.5***	3.5	0.0	2.8	18.3
Distance to equator (mm)	789	3.3	5.7	-17.3	4.8	14.3	295	0.0***	6.5	-18.0	0.8	13.3

Note: *** stands for the 1% (2-sided) significance level of the Mann-Whitney-U-test.
** stands for the 5% (2-sided) significance level of the Mann-Whitney-U-test.

Table 31: Crosstabulation of tumor location and radiation retinopathy

		Radiation retinopathy		
		Yes	**No**	**Total**
Location relative to fovea				
	Close to fovea	638 (80.8%)	190 (64.4%)	828 (76.3%)
	Far from fovea	152 (19.2%)	105 (35.6%)	257 (23.7%)
Location relative to optic disc				
	Close to optic disc	543 (68.7%)	135 (45.8%)	678 (62.5%)
	Far from optic disc	247 (31.3%)	160 (54.2%)	407 (37.5%)
Total		790 (100%)	295 (100%)	1085 (100%)

Table 32: Tumor size and location comparison between radiation optic neuropathy and no radiation optic neuropathy

Tumor characteristics	Radiation optic neuropathy						No radiation optic neuropathy					
	n	Mean	SD	Min	Median	Max	n	Mean	SD	Min	Median	Max
Size												
Prominence (mm)	472	3.9	1.7	0.0	3.6	14.1	613	4.3	2.3	0.7	3.6	14.0
Diameter (mm)	472	11.0	3.0	3.3	10.7	19.3	613	11.5	3.4	3.0	11.0	22.4
Volume (mm^3)	472	246.8	252.0	0	171	2535	613	325.7	396.5	3	185	2686
Location												
Distance to fovea (mm)	472	1.1	1.7	0.0	0.0	15.8	613	2.1***	3.2	0.0	0.9	18.5
Distance to optic disc (mm)	472	1.0	1.8	0.0	0.0	15.0	613	3.4***	3.2	0.0	2.8	18.3
Distance to equator (mm)	472	4.0	5.5	-17.3	5.3	14.2	612	1.3***	6.2	-18.0	2.3	14.3

Note: *** stands for the 1% (2-sided) significance level of the Mann-Whitney-U-test.

Table 33: Crosstabulation of tumor location and radiation optic neuropathy

		Radiation optic neuropathy		
		Yes	**No**	**Total**
Location relative to fovea				
	Close to fovea	387 (82.0%)	441 (71.9%)	828 (76.3%)
	Far from fovea	85 (18.0%)	172 (28.1%)	257 (23.7%)
Location relative to optic disc				
	Close to optic disc	398 (84.3%)	280 (45.7%)	678 (62.5%)
	Far from optic disc	74 (15.7%)	333 (54.3%)	407 (37.5%)
Total		472 (100%)	613 (100%)	1085 (100%)

Correlation between tumor size and location

As could be seen in the previous tables, tumors in the radiation-induced complication groups were – in part – significantly smaller and located much more posteriorly than the tumors of patients without any observed complication of that kind, whose mean tumor was larger in prominence, diameter and volume and located 0.3 mm anteriorly of the equator. To answer the question if there is a possible relationship between these two tumor features – that is size and location – an analysis was conducted of the correlation between all six continuous variables defining the tumor's size and location. Pearson's correlation coefficients are presented in table 34. The high correlation between the three tumor size variables is as expected, as is the negative correlation between the distance to the optic disc and fovea related to the equator, as it only reflects the anatomic realities with both structures at the very posterior pole of the eye. The most interesting finding however, is the strong negative relation between all three size variables and the tumor's distance to the equator. This provides an indication that in the present study cohort, the most anteriorly located melanomas were the largest in terms of thickness, diameter and volume, and the more posteriorly the tumor was located, the smaller it was in size. This can be an explanation for the previously reported result that patients who did not present a radiation-induced complication such as retinopathy or optic neuropathy had larger tumors, since those were located more anteriorly.

Table 34: Pearson correlation between tumor size and location

	Prominence	**Diameter**	**Volume**	**Distance to fovea**	**Distance to optic disc**	**Distance to equator**
Prominence	1	0.687***	0.898***	0.413***	0.338***	-0.618***
Diameter	0.687***	1	0.795***	0.206***	0.175***	-0.695***
Volume	0.898***	0.795***	1	0.377***	0.299***	-0.650***
Distance to fovea	0.413***	0.206***	0.377***	1	0.654***	-0.590***
Distance to optic disc	0.338***	0.175***	0.299***	0.654***	1	-0.489***
Distance to equator	-0.618***	-0.695***	-0.650***	-0.590***	-0.489***	1

Note: *** Correlation is significant with a p-value < 0.001.

4.3.1.3 Radiation parameters

Posterior segment complication versus no complication

Since tumors in the patient group that developed a radiation retinopathy or optic neuropathy were found to be significantly closer to the fovea and the optic disc, it is not surprising that also the mean proton dose on these structures were significantly higher than in the patient group without a posterior segment complication in the follow-up. Mean dose on the fovea differed by 10.9 CGE and mean dose on the optic disc even by 15.4 CGE between the two groups. The optic nerve itself was irradiated on a mean length of 1.3 mm in patients that suffered radiation retinopathy or optic neuropathy in the follow-up compared to 0.6 mm mean irradiated nerve length in the other patients. As expected, the ciliary body got irradiated on a sector 0.2 clock hours larger in the no-complication-group, though this difference was not significant, matching the findings that tumors in this group were found to be situated further anteriorly than the tumors in patients that developed a radiation retinopathy or optic neuropathy. All radiation parameters differed with a two-sided significance value $p<0.01$ in the Mann-Whitney-U-test.

Radiation retinopathy versus no radiation retinopathy

All radiation parameters except for radiated ciliary body sector in the analysis as shown in table 36 differed significantly between patients where a radiation retinopathy appeared after proton beam therapy and those patients where no such complication occurred (two-sided significance $p<0.01$ in the Mann-Whitney-U-test). In the former group, the mean dose on fovea and optic disc was by 10.4 CGE and 13.1 CGE greater, respectively, and the optic nerve got irradiated on 0.6 mm more length, whereas in the latter group the ciliary body got irradiated on a mean sector 0.2 clock hours larger. Also particularly noteworthy is the comparison of the median doses on fovea and optic disc. 50% of the patients developing a radiation retinopathy were irradiated with an average dose of 56 CGE or more on the fovea and 20.5 CGE or higher on the optic disc. In contrast to that, half of the patients without radiation retinopathy received average doses of 11 CGE or less on the fovea and 0 CGE on the optic disc.

Radiation optic neuropathy versus no radiation optic neuropathy

Radiation parameters in the radiation optic neuropathy group behave in the same way as previously presented for the radiation retinopathy group. Results are presented in table 37: In comparison to the patient cohort without any signs of radiation optic neuropathy, variables differ in the same manner and likewise significantly (two-sided significance $p<0.05$ in the Mann-Whitney-U-test). Most remarkable in this group is the even greater difference in the mean proton dose on the optic disc as well as in the irradiated optic nerve length. Whereas in the patient cohort with no evidence of radiation optic neuropathy, at least 50% did not get irradiated on the optic disc and nerve at all (median dose on optic disc: 0 CGE, median irradiated optic nerve length: 0 mm), half of the patients suffering from radiation optic neuropathy were irradiated with a mean dose of at least 59 CGE on the optic disc and on a mean optic nerve length of at least 2.2 mm (two-sided significance $p<0.001$ in the Mann-Whitney-U-test).

Table 35: Comparison of radiation parameters between posterior segment complication and no complication

	Radiation retinopathy/optic neuropathy						No radiation retinopathy/optic neuropathy					
Radiation parameters	n	Mean	SD	Min	Median	Max	n	Mean	SD	Min	Median	Max
Avg dose on fovea (CGE)	818	37.5	26.3	0	56	60	267	26.6***	27.9	0	7.0	75
Avg dose on optic disc (CGE)	818	28.8	27.6	0	21	65	267	13.4***	22.8	0	0.0	60
Avg radiated optic nerve (mm)	818	1.3	1.4	0.0	0.4	4.6	267	0.6***	1.1	0.0	0.0	4.2
Avg radiated ciliary body sector (clock hours)	817	2.6	1.5	0.0	2.4	10.8	267	2.8	1.8	0.1	2.5	11.4

Note: *** stands for the 1% (2-sided) significance level of the Mann-Whitney-U-test.

Table 36: Comparison of radiation parameters between radiation retinopathy and no radiation retinopathy

	Radiation retinopathy						No radiation retinopathy					
Radiation parameters	n	Mean	SD	Min	Median	Max	n	Mean	SD	Min	Median	Max
Avg dose on fovea (CGE)	790	37.6	26.3	0	56	60	295	27.2***	27.8	0	11	75
Avg dose on optic disc (CGE)	790	28.6	27.6	0	20.5	65	295	15.4***	24.1	0	0	60
Avg radiated optic nerve (mm)	790	1.2	1.4	0.0	0.3	4.6	295	0.7***	1.2	0.0	0.0	4.2
Avg radiated ciliary body sector (clock hours)	789	2.6	1.5	0.0	2.4	10.8	295	2.8	1.8	0.1	2.4	11.4

Note: *** stands for the 1% (2-sided) significance level of the Mann-Whitney-U-test.

Table 37: Comparison of radiation parameters between radiation optic neuropathy and no radiation optic neuropathy

	Radiation optic neuropathy						No radiation optic neuropathy					
Radiation parameters	n	Mean	SD	Min	Median	Max	n	Mean	SD	Min	Median	Max
Avg dose on fovea (CGE)	472	39.6	25.7	0	58	60	613	31.1***	27.7	0	37	75
Avg dose on optic disc (CGE)	472	40.6	25.4	0	59	65	613	13.0***	22.1	0	0	60
Avg radiated optic nerve (mm)	472	1.8	1.3	0.0	2.2	4.6	613	0.5***	1.1	0.0	0.0	4.2
Avg radiated ciliary body sector (clock hours)	471	2.7	1.5	0.1	2.5	10.8	613	2.6**	1.6	0.0	2.3	11.4

Note: *** stands for the 1% (2-sided) significance level of the Mann-Whitney-U-test.
** stands for the 5% (2-sided) significance level of the Mann-Whitney-U-test.

4.3.1.4 Radiation dose and risk of complications

As shown in the previous paragraph, the mean dose applied to the fovea and the optic disc differed significantly between patients with or without a manifestation of radiation retinopathy and radiation optic neuropathy, respectively. Therefore, the influence of these two variables, dose applied to the fovea and the optic disc, on the risk of complication was further examined.

Radiation retinopathy

Radiation retinopathy occurred very frequently in the patient group, even in almost two thirds of those that did not get irradiated on the macula at all, since this is only a small yet critical spot of the retina. However, as can be seen in table 38, the relative risk of this complication still rose significantly with increasing dose applied to the macula compared to no radiation to this structure at all (p-value for trend = 0.004). Radiation doses exceeding the level of 20 CGE were associated with an approximately 1.5-fold higher risk of radiation retinopathy. When it was possible to keep the radiation dose applied to the fovea below this level, the complication risk was not proven to be different to the basic risk associated with zero irradiation (95% CI: 0.838 – 1.403).

Figure 4 shows a linear increase in probability of retinopathy manifestation as a function of dose applied to the fovea. If the dose applied to the fovea increased by 10 CGE, the probability of developing a radiation retinopathy would rise by 3%, as calculated via linear regression. The basis risk associated with a radiation dose of 0 CGE to the macula was already quite high (63%) but still this risk could rise significantly and exceed rates of 80% when dosage to this structure increased.

The radiation dose on the optic disc also had a significant effect on the development of radiation retinopathy (p-value<0.001), with a relative risk rising with increasing dose up to an almost 2-fold high for doses above 50 CGE compared with the risk at zero irradiation of the optic disc.

Table 38: Risk of radiation retinopathy in dependence on dose applied to the fovea

Covariate	Level	No. at Risk	No. Events	RR (95% CI)
Dose to fovea	0 CGE (ref)	299	180	–
	1 – 20	120	86	1.085 (0.838 – 1.403)
	21 – 40	67	49	1.492 (1.087 – 2.046)
	41 – 50	42	35	1.592 (1.108 – 2.287)
	> 50	557	440	1.322 (1.111 – 1.572)
Dose to disc	0 CGE (ref)	465		–
	1 – 20	144		1.224 (0.981 – 1.528)
	21 – 40	59		1.507 (1.100 – 2.064)
	41 – 50	27		1.538 (0.977 – 2.421)
	> 50	390		1.973 (1.683 – 2.313)

RR = relative risk; CI = confidence interval

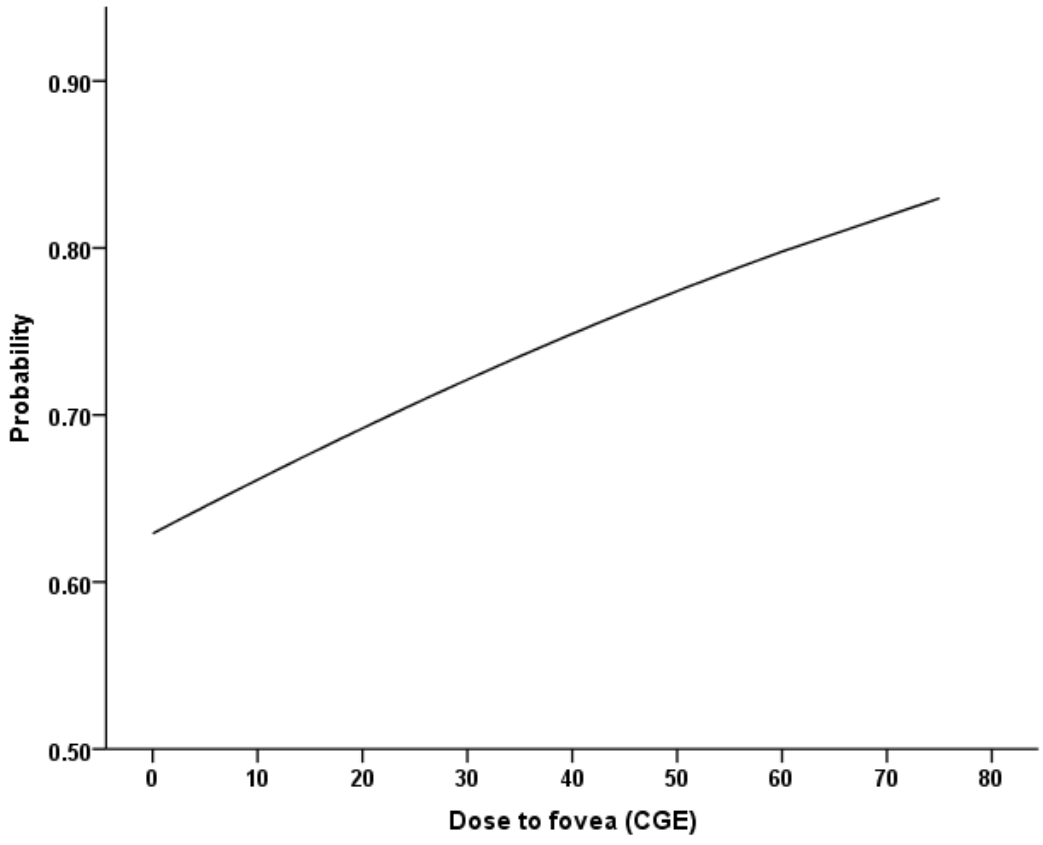

Figure 4: Probability of radiation retinopathy in dependence on dose applied to the fovea

Radiation optic neuropathy

The association between the dose applied to the optic disc and the manifestation of radiation optic neuropathy was a lot more distinct. As can be seen in table 39, the relative risk of development of optic neuropathy rose sharply with increasing dose applied to the optic disc ($p<0.001$), in comparison to incidence rates after no radiation onto this structure (0 CGE). When the optic disc got irradiated with doses exceeding 50 CGE, the associated risk of optic neuropathy diagnosis was nearly 9-fold higher than the risk after zero radiation. Figure 5 shows a linear relation between the dose applied to the optic disc and the probability of developing radiation optic neuropathy, characterized by an even steeper slope than seen in figure 4, regarding radiation retinopathy. An increase of dosage by 10 CGE to the optic disc resulted in a 9% higher probability of developing optic neuropathy. The basic risk related to zero irradiation to this sensitive structure was 20.6%.

Radiation energy to the macula above 0 CGE was also related with a slightly higher risk of optic neuropathy manifestation when compared with no radiation at all ($p=0.002$), though with no linear rise in relative risk observable as the dose applied to this structure increases.

Table 39: Risk of radiation optic neuropathy in dependence on dose applied to the optic disc

Covariates	Level	No. at Risk	No. Events	RR (95% CI)
Dose to disc	0 CGE (ref)	465	80	–
	1 – 20	144	58	2.289 (1.632 – 3.210)
	21 – 40	59	25	3.252 (2.071 – 5.105)
	41 – 50	27	17	6.092 (3.597 – 10.320)
	> 50	390	292	8.762 (6.806 – 11.280)
Dose to fovea	0 CGE (ref)	299		–
	1 – 20	120		1.110 (0.783 – 1.573)
	21 – 40	67		1.637 (1.100 – 2.436)
	41 – 50	42		1.393 (0.859 – 2.260)
	> 50	557		1.561 (1.234 – 1.974)

RR = relative risk; CI = confidence interval

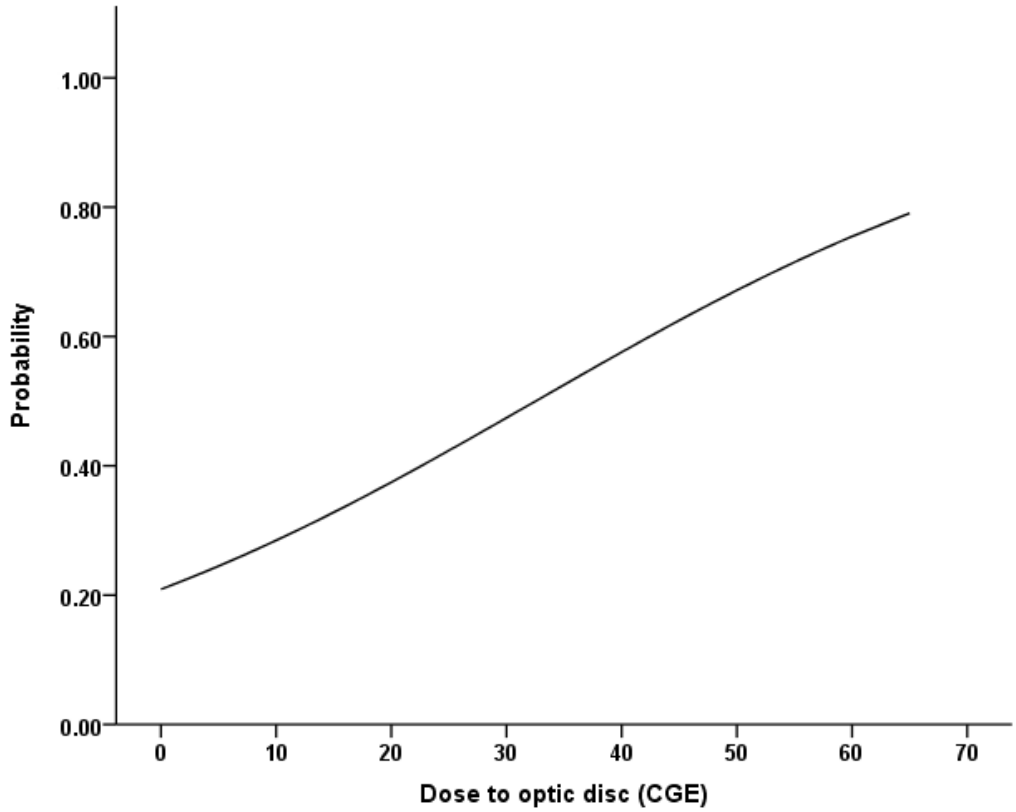

Figure 5: Probability of radiation optic neuropathy in dependence on dose applied to the optic disc

4.3.2 Multivariate analysis

After detecting significant differences in the tumor characteristics and radiation parameters between the subgroups regarding radiation-induced complications in the previous univariate analysis, the following paragraph examines factors determining the appearance of the two complications in question. Therefore, all those variables verified as significant in the univariate analysis were entered into a multiple logistic regression analysis to examine a possible combined influence on the manifestation of radiation retinopathy and optic neuropathy, respectively. Results of the multiple regression analysis are presented in tables 40 and 41.

With regards to the development of radiation retinopathy, the only variable detected to be influential was the melanoma's distance to the equator, with a more posterior location being predictive for this complication (p-value = 0.001).

Table 40: Multiple logistic regression analysis for the occurrence of radiation retinopathy

Variables	B	Standard error	Wald	df	p-value	Exp(B)
Tumor diameter	0.091	0.055	2.745	1	0.098	1.096
Tumor volume	0.000	0.000	0.287	1	0.592	1.000
Distance to fovea	0.002	0.052	0.001	1	0.975	1.002
Distance to optic disc	0.011	0.050	0.050	1	0.823	1.011
Distance to equator	0.079	0.023	11.574	1	**0.001**	1.082
Avg Dose on fovea	0.006	0.004	2.400	1	0.121	1.006
Avg dose on optic disc	0.018	0.009	3.716	1	0.054	1.018
Avg radiated optic nerve length	0.006	0.176	0.001	1	0.974	1.006

Concerning radiation optic neuropathy, multiple regression analysis detected that several factors were significantly predictive of its occurrence, namely the tumor's distance to the optic disc and the equator – again in the direction of a more posterior location – , as well as mean radiation doses onto fovea, optic disc and ciliary body. In the latter case this influence was negative, supporting even more the impact of a posterior tumor location and focus of radiation.

Table 41: Multiple logistic regression analysis for the occurrence of radiation optic neuropathy

Variables	B	Standard error	Wald	df	p-value	Exp(B)
Distance to fovea	0.124	0.069	3.276	1	0.070	1.132
Distance to optic disc	-0.156	0.063	6.069	1	**0.014**	0.856
Distance to equator	0.046	0.020	5.215	1	**0.022**	1.047
Avg Dose on fovea	0.013	0.005	7.384	1	**0.007**	1.013
Avg dose on optic disc	0.037	0.008	19.008	1	**0.000**	1.037
Avg radiated optic nerve length	-0.065	0.148	0.194	1	0.660	0.937
Irradiated ciliary body sector	-0.128	0.065	3.861	1	**0.049**	0.880

4.4 Visual acuity results

4.4.1 Initial visual acuity

Before the start of proton beam therapy, the patients' mean visual acuity was 0.408 logMAR, ranging from hand motion (HM) only to very good test results as good as -0.1 logMAR which equals 1.2 in DIN. Half of the patients achieved a test result of 0.3 logMAR and better.

Table 42: Visual acuity prior to proton beam therapy

Initial visual acuity (logMAR)	n=1085
Mean	0.408
Median	0.300
Minimum	HM
Maximum	-0.1

Visual acuity and tumor stage

Initial visual acuity differed significantly between the tumor stages (two-sided significance $p<0.001$ in the Kruskal-Wallis-test). Tumors in earlier stages were correlated with a better visual acuity of the patient prior to proton beam therapy. Patients with tumors of stage 1 had a mean initial visual acuity of 0.316 logMAR, whereas patients with the diagnosis of a stage 4 tumor reached visual acuity levels of only 0.717 logMAR.

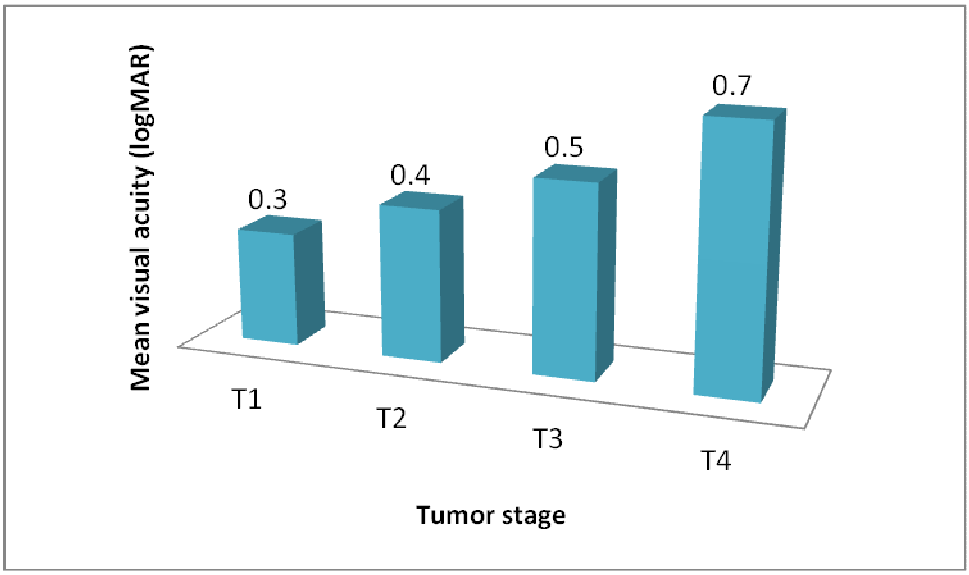

Figure 6: Mean initial visual acuity by tumor stage in logMAR

Visual acuity and tumor location

The patients' mean initial visual acuity differed significantly depending on the tumor location. If the tumor was located close to either the fovea or the optic disc, this was associated with a mean visual test result of 0.44 logMAR each and thus worse than the visual acuity of patients with tumors situated far from these structures (two-sided significance $p<0.001$ in the Mann-Whitney-U-test).

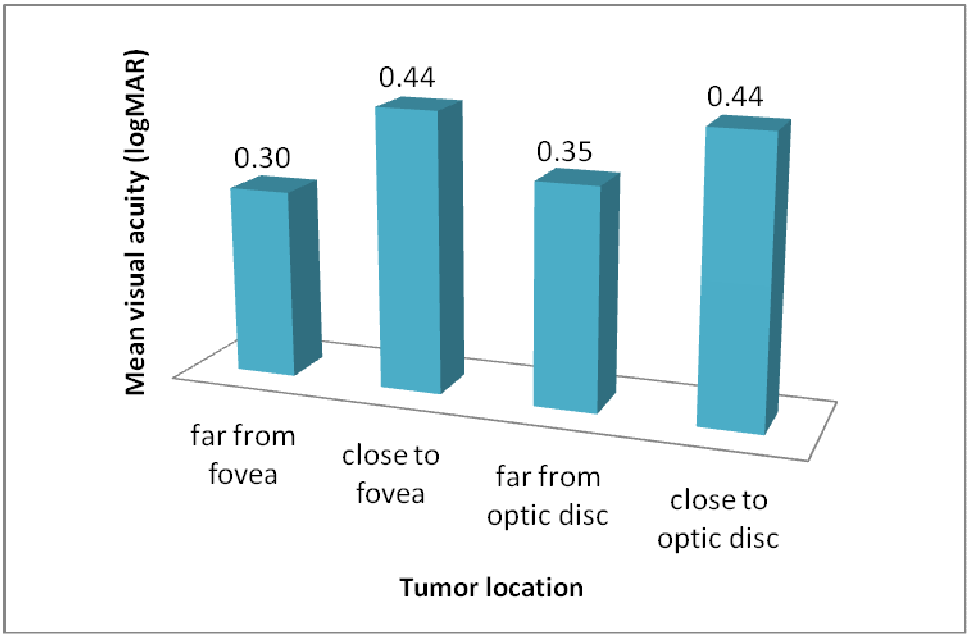

Figure 7: Mean initial visual acuity by tumor location in logMAR

4.4.2 Visual outcome

At the end of the observation period the patients' mean visual acuity tested on the last documented examination was 1.126 logMAR, ranging from no light perception (NLP) to -0.1 logMAR. Fifty percent of the examined patients had visual acuity test results of 1.2 logMAR and worse.

Table 43: Visual acuity at last examination

Final visual acuity (logMAR)	**n=1085**
Mean	1.126
Median	1.2
Minimum	NLP
Maximum	-0.1

Posterior segment complication versus no complication

The latest visual test results of the patients with a diagnosed radiation retinopathy or optic neuropathy were significantly worse than those of the patients that did not present a posterior segment complication of that kind (two-sided significance $p<0.001$ in the Mann-Whitney-U-test). While visual acuity on the last follow-up in both groups ranged widely from no light perception at all to very good results of 0.0 logMAR and better, 50% of the patients with a diagnosed radiation retinopathy or optic neuropathy had visual test results of 1.3 logMAR, whereas the median visual acuity level in the group of patients without such posterior segment complication was 0.5 logMAR and thus significantly better. Since both groups started from the same initial value, with the median visual acuity prior to radiation being 0.3 logMAR in each group, it can be reasonably concluded that the significant visual impairments observed in this study population may be attributable to the manifestation of a radiation retinopathy and/or optic neuropathy. It is noteworthy that also the observation time and hence the time of the last documented visual test result differed significantly between both groups. Patients that were diagnosed with radiation retinopathy or optic neuropathy after proton beam therapy were almost 1.5 years longer in the follow-up than those patients who remained complication-free.

Table 44: Comparison of visual acuity development between posterior segment complication and no complication

	Radiation retinopathy/optic neuropathy	
Development of visual acuity	**Yes (n=818)**	**No (n=267)**
Initial visual acuity (logMAR)		
Mean	0.407	0.411
Median	0.300	0.300
Range	HM – -0.1	HM – -0.1
Final visual acuity (logMAR)		
Mean	1.259	0.719***
Median	1.3	0.495
Range	NLP – 0.0	NLP – -0.1
Time of final visual test (months)		
Mean (±SD)	58.0 (±32.5)	31.3*** (±21.1)
Median	52.1	25.0
Range	12.4 – 170.4	12.0 – 144.4

Note: *** stands for the 1% (2-sided) significance level of the Mann-Whitney-U-test.

Radiation retinopathy versus no radiation retinopathy

With the focus on radiation retinopathy as the radiation complication of interest, comparison of the visual outcome between patients affected and those not affected reached the same results. Median visual acuity levels on the last follow-up were again 1.3 logMAR in those affected and 0.5 logMAR in the comparison group. Mean levels differed not quite as much as before, but still significantly (two-sided significance $p<0.001$ in the Mann-Whitney-U-test), with the mean final visual acuity of 0.749 logMAR in patients without radiation retinopathy being slightly worse than the mean visual outcome in patients without any posterior segment complication at all, probably due to the former cohort now also comprising patients who solely suffered from radiation optic neuropathy. Once again visual acuity prior to proton beam therapy did not differ between the two groups of concern but the time of the last visual test result did in the same manner as already noted.

Table 45: Comparison of visual acuity development between radiation retinopathy and no radiation retinopathy

	Radiation retinopathy	
Development of visual acuity	**Yes (n=790)**	**No (n=295)**
Initial visual acuity (logMAR)		
Mean	0.408	0.410
Median	0.300	0.300
Range	HM – -0.1	HM – -0.1
Final visual acuity (logMAR)		
Mean	1.267	0.749***
Median	1.3	0.500
Range	NLP – 0.0	NLP – -0.1
Time of final visual test (months)		
Mean (±SD)	58.4 (±32.5)	33.0*** (±23.0)
Median	52.2	25.6
Range	12.6 – 170.4	12.0 – 144.4

Note: *** stands for the 1% (2-sided) significance level of the Mann-Whitney-U-test.

Radiation retinopathy solely

Of the 790 patients with a diagnosed radiation retinopathy, 346 patients showed signs of this complication only and no radiation optic neuropathy in the follow-up. Their visual acuity results are presented in table 46. While initial visual acuity was again almost identical to the values mentioned earlier, it can be seen that the final visual acuity in patients who presented only signs of radiation retinopathy, was a lot better than the visual outcome in the patient group that also comprised those who were additionally diagnosed with optic neuropathy, as presented in table 45. Half of the patients with radiation retinopathy solely had a final visual acuity of 1.0 logMAR or better compared to 1.3 logMAR in the group before that, almost 50% of which consisted of radiation optic neuropathy patients. This observation suggests that the development of radiation optic neuropathy worsens the patient's visual acuity yet a lot more than does radiation retinopathy alone.

Table 46: Visual acuity development in patients with radiation retinopathy solely

Development of visual acuity	**Radiation retinopathy solely (n=346)**
Initial visual acuity (logMAR)	
Mean	0.394
Median	0.300
Range	CF – -0.1
Final visual acuity (logMAR)	
Mean	0.969
Median	1.0
Range	NLP – 0.0
Time of final visual test (months)	
Mean (±SD)	48.4 (±28.2)
Median	52.2
Range	12.6 – 170.4

In 190 patients of those with radiation retinopathy solely, documentation on the possible presence of a macular edema was available. The table 47 below shows a comparison of the final visual acuity results for those retinopathy patients with a macular edema versus without any macular edema in the follow-up. It can be seen that the difference in visual outcome between those two patient groups was basically of no significance. Mean values were almost identical. Median values suggest a slightly better visual outcome in patients with no macular edema (0.9 logMAR compared to 1.0 logMar).

Table 47: Comparison of final visual acuity between macula edema and no macula edema in the scope of radiation retinopathy

	Macular edema	
Final visual acuity (logMAR)	**Yes (n=107)**	**No (n=83)**
Mean	0.994	0.967
Median	1.0	0.9
Range	NLP – 0.1	NLP – 0.0

Radiation optic neuropathy versus no radiation optic neuropathy

Even worse final visual acuity levels were observed in patients with a manifestation of radiation optic neuropathy during the observation period, which supports the aforementioned hypothesis. Mean visual acuity on the last follow-up in this group was 1.471 logMAR and 50% of the patients diagnosed with radiation optic neuropathy achieved results below or equal to 1.5 logMAR. Compared to the group without optic neuropathy, these final visual acuity levels are significantly worse. Looking at the patients with no such complication, half of the group reached visual acuity of 0.7 logMAR and better on the last documented examination date (two-sided significance $p<0.001$ in the Mann-Whitney-U-test). Consequently, radiation optic neuropathy can be regarded as the major vision-limiting complication of the two complications investigated.

Table 48: Comparison of visual acuity development between radiation optic neuropathy and no radiation optic neuropathy

	Radiation optic neuropathy	
Development of visual acuity	**Yes (n=472)**	**No (n=613)**
Initial visual acuity (logMAR)		
Mean	0.417	0.402
Median	0.300	0.300
Range	HM – -0.1	HM – -0.1
Final visual acuity (logMAR)		
Mean	1.471	0.860***
Median	1.500	0.700
Range	NLP – 0.0	NLP – -0.1
Time of final visual test (months)		
Mean (±SD)	65.1 (±33.7)	40.9*** (±26.7)
Median	58.7	34.2
Range	12.4 – 161.0	12.0 – 170.4

Note: *** stands for the 1% (2-sided) significance level of the Mann-Whitney-U-test.

5. Discussion

Radiation therapy with proton beams is a well established treatment for choroidal melanomas. It is effective in achieving high tumor control, with rates comparable to the radical surgical intervention, i.e. enucleation of the affected eye bulb. The huge advantage of radiotherapy treatment therefore lies in the possibility for the patient to keep his eye globe and thus sight. With the preservation of the eye, the focus now shifts to complications arising from radiation of healthy tissues, which is inevitable in any radiotherapy if one doesn't want to jeopardize tumor control. Two important complications after irradiation of the posterior eye segment are radiation-induced retinopathy and optic neuropathy, since these may hugely compromise the patient's visual ability long after proton therapy. One big advantage of proton radiation as a conservative therapeutic strategy is, however, the possibility to maintain the patient's vision. Thus, these complications should not be underrated. This study concentrated on the incidence rates of both posterior segment complications and the effect they have on the patient's visual outcome. Furthermore, its aim was to unveil the crucial factors, in particular with regards to tumor characteristics, which have the biggest impact on the development of both radiation retinopathy and optic neuropathy.

5.1 Summary of the main results

In this study group, 72.8% of the patients presented with radiation retinopathy and 43.5% of the irradiated patients presented with optic neuropathy in the follow-up, manifesting itself after a median of 21.6 months since proton beam radiotherapy. Annual rates peaked in the second year post-irradiation regarding both complications. Concerning tumor characteristics as an influence factor on the appearance of a posterior segment complication, univariate statistical analyses showed that tumors were more often smaller in diameter and volume and in particular, significantly closer to the posterior pole, the optic disc and the fovea in patients who developed a radiation-induced retinopathy. Optic neuropathy was also associated with tumors significantly closer to the optic disc and fovea and thus more posteriorly located. This finding is consistent with the result that radiation dosage was significantly higher on these structures in the neuropathy as well as retinopathy patients. Above all, an increase in radiation dose on the optic disc was associated with a significantly higher risk of optic neuropathy. Probability of this complication rose in a linear fashion with increasing radiation dose applied to the optic disc. Regarding retinopathy, incidence rates were already high even if the macula did not receive any irradiation but still rates increased with increasing dose applied to this structure. When

investigating their combined influence in the multivariate analysis, parameters that had an impact on the occurrence of radiation retinopathy were solely the tumor's distance to the equator. A tumor location closer to the posterior pole therefore increased the probability of developing a retinopathy. Analysis of the impact parameters on optic neuropathy manifestation in the multiple regression revealed that the closer the tumor was to the posterior pole and the optic disc and the higher the dose applied to the macula, optic disc and posterior segment as opposed to the ciliary body and anterior segment, the higher the probability of this radiation-induced complication.

Manifestation of one of the two posterior segment complications was associated with a significant impairment of visual acuity, with optic neuropathy being the major contributor to a loss of visual function. When patients presented with optic neuropathy during follow-up, the median visual acuity on their last follow-up was 1.5 logMAR. If they developed radiation-induced retinopathy solely, visual function was also significantly worse than without any complication but with a median visual outcome of 1.0 logMAR not as bad as in case neuropathy occurred. Therefore, optic neuropathy is the more limiting factor for visual outcome when compared with radiation retinopathy.

5.2 Strengths and weaknesses

The main strength of this study is its large study population of 1085 patients drawn from all choroidal melanomas that were treated with proton beam radiotherapy at the Helmholtz Institute since 1998 considering some exclusion criteria for better comparability. This is accompanied by a years' experience of the Department of Ophthalmology at the Charité – Universitätsmedizin Berlin in the treatment of choroidal melanomas with proton beam radiotherapy, making for uniformity of the treatment process and limiting any bias to a minimum. Detectable differences in the patients' outcomes should therefore be only due to differences in the patients themselves, their tumors and the resulting irradiation and not to any difference in the treatment or examination procedure. The very long follow-up period going back almost 15 years at maximum is another huge strength of this study. It allows for better measurement of more reliable and realistic incidence rates of radiation retinopathy and optic neuropathy, since also those events are registered that would not have been covered by studies with a shorter follow-up and thus it permits new insights into how long after proton therapy these complications may indeed still occur.

Looking at the study design, one of the study's major limitations lies in its retrospective nature and the lack of information about general diseases such as diabetes and arterial hypertension.

This again is an effect of the retrospective nature, as medical records were often insufficient concerning data on general diseases. Since especially diabetes and arterial hypertension are associated with a proven increased risk of radiation-induced complications in these patients, these risk factors should ideally have been taken into account in the univariate and multivariate analysis but were omitted due to missing data in the medical records [90, 97, 119].

5.3 Incidence rates

The total 5-year incidence rates determined for the present study population were 86.1% for radiation retinopathy and 52.5% for radiation optic neuropathy. Up until now, there are only few reports in literature on the incidence of radiation retinopathy and optic neuropathy in choroidal melanomas after radiation treatment and even fewer reports on rates post-proton beam therapy [85, 89, 90, 119-122]. In a retrospective study with 21 patients with particularly large choroidal melanomas of a tumor thickness of at least 8 mm or a basal diameter of at least 16 mm , Conway et al. found radiation retinopathy and radiation optic neuropathy to occur in 9.5% of the patients each at 24 months follow-up [85]. Another small study from Kaushik et al., though on patients with orbital/ocular lymphoma, observed radiation retinopathy in 12% of the cases after external beam radiotherapy (median observation time: 36.5 months) [121]. Several authors report posterior segment complication rates after plaque brachytherapy. Shields et al. observed development of retinopathy and papillopathy in 25% and 22% of 354 patients, respectively, with large uveal melanomas after ^{125}I brachytherapy and 24 months' observation time [122]. Shields and other colleagues again found similar incidence rates in children with retinoblastoma who underwent plaque radiotherapy [123]. Higher rates were reported by Bechrakis et al., who detected radiation retinopathy in two thirds of 152 uveal melanomas after ^{125}I brachytherapy and a mean follow-up of 27 months [120]. Finger could find a radiation retinopathy development in only 4% of anteriorly located melanomas and 52% of posterior pole melanomas after plaque radiation therapy and a mean follow-up of 42 months [89]. Compared to the incidence rates detected in the present study, these rates reported after plaque radiotherapy seem to be much lower. This might be due to the rather small study cohorts and short observation time in all the above-mentioned studies, when compared to the 1085 patient comprising the study group of this work which was observed for a mean time of 54.4 months (median: 48.1 months). Yet, Gündüz et al. observed 1300 patients with posterior choroidal melanomas after plaque radiotherapy for a median observation time of 61 months and detected radiation retinopathy in 43.1% of the patients, with their calculated 5-year-incidence rates being 42% and 8% for non-proliferative

retinopathy and proliferative retinopathy, respectively, and thus again much lower than those estimated in the present study [90]. At the Department of Ophthalmology of the Charité – Universitätsmedizin Berlin, a central tumor location is the main medical indication for a therapy using proton beam irradiation. Those tumors require a special protection of the sensitive structures in a way, which may be best achieved by the characteristic dose deposition of proton beams. Brachytherapy with the use of ruthenium plaques is usually performed in peripheral tumors below a prominence of 6 mm. For tumors with a greater thickness, proton radiotherapy is again the treatment method of choice. However, in this study, all patients who underwent endoresection of the tumor after proton radiotherapy were excluded, an intervention which is almost exclusively required in thick tumors with extensive exudation [124]. Centrally located tumors are in general detected much sooner due to early visual strain and are thus usually smaller. Hence, the present study comprises a large number of high risk patients, characterized by a tumor of a central location. Accordingly, a meaningful comparison between the patient group this study reports on and others from the above-mentioned literature would not be easily feasible.

The major risk factor for the development of a radiation-induced retinopathy is a central tumor growth at the posterior eye pole and for the development of radiation optic neuropathy, a direct attachment of the tumor to the optic disc. Based on this knowledge, the high incidence rates for both complications reported in this study become clearer and are not that surprising after all. Even higher rates were previously published by Riechardt et al. who observed 5-year incidence rates of 90.3% for radiation retinopathy and 89.6% for radiation-induced optic neuropathy in parapapillary melanomas post proton beam therapy [125]. Furthermore, Kim et al. found approximately two thirds of parapapillary choroidal melanomas developing papillopathy after proton beam irradiation, supporting the explanation of very high rates in high risk tumors, characterized by a central and disc-close location [126].

Comparison with brachytherapy

In brachytherapy, radiation is delivered from the plaque affixed directly on the episclera over the base of the tumor. To achieve the necessary dosage at the tumor apex, the tumor base will receive very high irradiation energy as will the retina immediately surrounding the tumor, due to the relatively less sharp energy profile when compared to proton beam irradiation. When irradiating melanomas of a posterior location, it would therefore be a logical consequence to observe more frequent and severe radiation retinopathy and optic neuropathy in brachytherapy [60]. There are only a few comparative studies on plaque radiotherapy versus proton therapy,

and those concentrate on the outcome in terms of tumor control, not radiation complications [127, 128]. As already mentioned in the previous paragraph, the few existing reports on incidence rates post proton beam therapy or post brachytherapy describe rates of radiation retinopathy and optic neuropathy to be in fact somewhat lower after plaque radiotherapy than after irradiation with protons. This is most likely due to the generally accepted treatment regime of choroidal melanomas of different size and location also followed by the Department of Ophthalmology of the Charité – Universitätsmedizin Berlin. Brachytherapy is acknowledged to be the method of choice for tumors with a thickness of 6 mm or less and a distance to the optic disc and fovea of at least 3 mm. Juxtapapillary melanomas located within less than 3mm proximity of the optic disc or fovea require the radio physical features of proton beam therapy. Also for larger tumors of a thickness above 6 mm, proton therapy is the treatment of choice [2, 62]. It is worth noting that, in a work from 2013, Lipski and colleagues exemplarily describe the dose deposition situation in the radiation plan simulation for a parafoveal tumor compared between ruthenium plaque- and proton radiotherapy. While in the proton therapy simulation the fovea would lie outside the radiation field, in the plaque radiotherapy simulation this structure would receive a significant dosage. With increasing tumor thickness, the dose on the fovea would be even greater and the radiation field would also include the optic disc, whereas in the irradiation plan for proton therapy both structures would still lie outside of the radiation field [2]. Keeping in mind that a posterior tumor location and close proximity to the optic disc and fovea are the main risk factors for the development of radiation retinopathy and optic neuropathy, this may explain why lower complication rates have been observed after plaque radiotherapy. This mode of treatment is often used in more peripheral tumors, although also central ones and even juxtapapillary tumors might be treated by plaque radiotherapy, in which case optic neuropathy incidence rates are actually comparably high [126, 129]. However, achieving local tumor control, especially in melanomas close to the optic disc remains challenging when additionally striving for the best visual outcome. Furthermore, functional results of patients will be very poor if the fovea, the optic disc or both are directly irradiated when using brachytherapy treatment. Vision loss will then occur very soon after suturing the radiating plaque onto the tumor base, raising the question of the justification of radiation-induced complications in already “dead” eyes. Another reason for biased results are the varying treatment regimes used by different ophthalmic clinics in dealing with radiation complications. Whereas some practitioners perform prophylactic anti-VEGF injections, others like the Department of Ophthalmology of the Charité – Universitätsmedizin Berlin, offer patients the opportunity to participate in a randomized trial comparing laser photocoagulation with anti-VEGF injections. Therefore, no comparable pure

incidence rates after proton and plaque radiotherapy are to be expected anymore from future studies.

Comparison with stereotactic surgery

Plaque radiotherapy and proton beam irradiation have already been in use for a long time as the most common treatment choices for choroidal melanomas having replaced the enucleation as first choice. The stereotactic radiosurgery with the "CyberKnife®" or "Leksell gamma knife®" is one of the newer treatment modalities, allowing for treatment in a single session and without need to use the elaborate proton accelerator. With steep dose gradients, making a precise dose delivery even to small targets possible, the physical properties of SRS make for better damage minimization to healthy tissue compared to classical stereotactic radiotherapy [130-132]. As this therapy mode is still young, little data on therapy outcome is still available, but first studies suggest a tumor control rate equal to plaque radiotherapy and proton beam therapy [71, 132, 133]. Reports on radiation complications are even fewer, but they also suggest high or even higher incidence rates of radiation retinopathy and optic neuropathy compared to proton beam therapy. In a study of 32 patients with choroidal melanomas treated with a single-fraction Leksell gamma knife radiosurgery with a median marginal dose of 50 Gy, Hass et al. observed radiation retinopathy in 84% of the patients during a mean follow-up of 38 months [130]. The large majority of their patients were treated for either juxtapapillary or parafoveal melanomas. Rennie et al. found development of radiation retinopathy in 11 of 14 (79%) choroidal melanoma patients after a mean follow-up of 24 months after a single-fraction gamma knife treatment with 70 Gy [134]. Nevertheless, it remains to be seen if more longtime – preferably comparable – studies will confirm these results regarding the effects of the stereotactic surgery on healthy tissues such as fovea, optic disc and nerve.

5.4 Patient characteristics and follow-up

5.4.1 Patient gender and age

In this study, women developed a posterior segment complication slightly more often than men (78.3% versus 72.6%). With no evidence in the literature on gender differences regarding radiation retinopathy or optic neuropathy development, this finding could very likely be a bias, as incidence rates differ only by a small amount. However, one could also presume that women

are more health-conscious and pursue their follow-up more diligently than men and are therefore more likely to be diagnosed with a posterior segment complication.
Similar arguments could be raised to explain the finding that patients with a posterior segment complication manifestation were younger. Patient age was 59.9 years versus 63.2 years and though statistically significant, this small difference in age is rather negligible.

5.4.2 Observation period

Both patients with the diagnosis of a radiation retinopathy and those with manifested optic neuropathy were significantly longer in the follow-up than patients without any such complication. The mean observation period in both cases differed by more than two years (61.5 versus 35.3 months and 69.4 versus 42.8 months). With proton beam therapy being feasible only at a few centers worldwide, the catchment area of such a treatment facility is very large. At the Department of Ophthalmology of the Charité – Universitätsmedizin Berlin, patients treated with proton beam radiation are referred to the Clinic for the treatment of their choroidal melanoma not only from all over Germany but also from other European countries. Therefore, many patients who have to travel long distances, will sooner or later relocate their medical aftercare to their local ophthalmologist. Especially if the follow-up examinations run smoothly and no severe complication occurs during several years of observation at the Department of Ophthalmology of the Charité – Universitätsmedizin Berlin. It should be emphasized that first appearance of radiation retinopathy and optic neuropathy was after a mean time of 23.0 months and 25.6 months, respectively. Patients with no diagnosis of that kind stayed in the follow-up at the Charité – Universitätsmedizin Berlin for as long as 35.3 months and 42.8 months, respectively. This exceeds the mean latency for a complication development and supports the outlined hypothesis. On the other hand, if such a complication had been diagnosed during the first years of check-up at the Charité – Universitätsmedizin Berlin, it is very likely that these patients would have chosen to remain in the hands of a highly specialized and advanced level university clinic for their follow-up examinations and treatment of this complication. This surely is a plausible explanation for the significantly longer follow-up times of 61.5 months and 69.4 months observed for patients with retinopathy and optic neuropathy, respectively.

5.5 Predictive factors

5.5.1 Tumor location

For the development of both radiation-induced retinopathy and optic neuropathy, a tumor location closer to the posterior eye segment was found to be a significant risk factor not only in the univariate but also in the multivariate analysis. Furthermore, a close proximity to the optic disc was of significant influence especially for the manifestation of an optic neuropathy but also of a radiation retinopathy, though in the latter, this was the case only in the univariate model. These findings are consistent with those already published by previous investigators. As already mentioned, Finger found that only 4% of anteriorly located melanomas but 52% of posterior pole melanomas developed radiation retinopathy [89]. In a later study, Finger and colleagues observed the same impact of a posterior pole location on the appearance of radiation maculopathy, with a calculated relative risk of 6.66 compared with anterior location [135]. Shorter tumor distance to the optic disc was found to be a risk factor for the development of radiation retinopathy not only by Gündüz et al. but for the proliferative form also by Boldt et al. and Bianciotto et al. [90, 136, 137]. Also the very high rates of both radiation retinopathy and optic neuropathy detected by Riechardt et al. in parapapillary melanomas confirm the common recognition of the tumor's proximity to the optic disc as being a major risk factor for both complications [125]. The results of the retrospective investigation of choroidal melanomas located within 0 to 1 disc diameters of the optic disc by Kim and colleagues, who observed radiation-induced optic neuropathy in 68% of the patients also support this finding [126]. Patients presenting with parapapillary melanomas, with location at the posterior pole and involvement of the optic disc, are among the highest risk patients for radiation-induced complications, especially optic neuropathy. The present study's findings agree with the literature describing a posterior tumor location as a major risk factor for the development of radiation retinopathy and optic neuropathy or – to be more precise – a closer tumor distance to the optic disc, especially for developing optic neuropathy.

5.5.2 Tumor size

It is believed that irradiation of larger tumors will result in higher complication rates such as retinopathy and optic neuropathy, since they require more irradiation, resulting in an increased dose being delivered to all ocular structures [60, 90, 138]. Larger tumor base will increase the spill-over energy absorbed by the surrounding retina, resulting in a higher incidence of

retinopathy after radiation [90]. In fact, Finger et al. could observe that a tumor thickness above 6 mm is associated with a 4.5-fold risk of radiation maculopathy compared with a height less than 3 mm in choroidal melanomas treated with plaque radiation, suggesting it to be a risk factor for the development of a radiation complication. Regarding the tumor diameter, they found no significant impact on radiation maculopathy in the multivariate model, though in the univariate comparison analysis tumors were larger in diameter in the radiation complication group [135]. Gündüz et al. reported almost identical results. They also found a tumor base of greater than 10 mm and a thickness of greater than 5 mm to be major risk factors predictive of the appearance of radiation retinopathy after ^{125}I brachytherapy, once again the tumor base was only predictive in the univariate analysis [90]. In the current study, there was no significant influence of the tumor size on the development of radiation retinopathy or optic neuropathy in the multivariate regression. If there was any observation made, it seems to be quite the opposite to what was expected in the light of the literature and theory. In this study, tumors in the group of patients without a diagnosed radiation complication were in fact even larger in prominence, diameter and volume. If we take a closer look at the Pearson table of correlation between tumor size and location presented further above and the previous explanations on the impact of the tumor location, this finding becomes very clear. In the present study population, an increase in tumor size was strongly correlated with a more anterior location of the tumor, further away from the posterior segment and its sensitive structures. As mentioned above, this matches the treatment regime of the Department of Ophthalmology of the Charité – Universitätsmedizin Berlin, which is used for treating those choroidal melanomas with proton beam therapy that are either centrally located at the posterior pole, and in that case rather small, or located in the periphery or anteriorly and whose thickness is above 6 mm. Bearing in mind the previous finding that the major predictor for the appearance of both radiation retinopathy and optic neuropathy was a posterior tumor location, this might give an explanation for the observations on tumor size. Melanomas in the cohort without any complication were found to be larger, because they were situated considerably more anteriorly. This result further underlines the impact of tumor location close to the posterior eye pole on the development of a posterior segment complication. In other words, it supports the somewhat protective effect of an anterior tumor location, as anteriorly located tumors were larger and will thus have received higher radiation doses and still they resulted in fewer radiation-induced complication rates, assuming that those tumors are at a rather high risk of toxic tumor syndrome. A similar observation and conclusion was made and drawn by Finger in the already mentioned study on choroidal melanomas after plaque radiotherapy [89].

5.5.3 Radiation dose

The explanation for the strong impact of a posterior segment and above all closeness of the tumor to the optic disc on the manifestation of radiation-induced complications evidently lies in the resulting higher radiation doses deposited onto the posterior retina including the macula and the optic disc and thus the higher damage. As a logical consequence, radiation dose applied to this segment and its sensitive structures should be a significant risk factor itself. Indeed, this study reports significant differences in radiation dose applied to the macula, optic disc and nerve in the univariate group comparison between patients who presented with radiation retinopathy or optic neuropathy and those who did not. For optic neuropathy, this work could additionally detect the dose applied to the macula and optic disc to be predictive factors in the multivariate regression analysis. These findings are in agreement with the literature on radiation dose as a risk factor for radiation vasculopathy such as retinopathy including maculopathy and optic neuropathy [91, 139, 140]. Reports include increasing rates of radiation maculopathy with increasing dose applied to the macula [119, 135, 141], high optic disc dose as a significant risk factor predictive of radiation optic neuropathy [119, 142], as well as a high dose applied to the tumor apex and base in brachytherapy determining the incidence of radiation retinopathy including maculopathy [90, 142].

Furthermore, the present study reports a strong correlation between irradiation doses on the macula and optic disc on the one hand and the probability of onset of a radiation retinopathy and optic neuropathy, on the other. In optic neuropathy, a sharp linear dose-response relationship could be detected, with probabilities being 20.6% for 0 CGE irradiation and getting as high as nearly 80% for optic disc dosage of 65 CGE. The relative risk of radiation retinopathy also increased linearly with increasing dose applied to the macula, however being high already at zero irradiation, when radiation retinopathy is likely to occur even in almost two thirds of those that did not get irradiated on the macula at all. As mentioned earlier, multiple regression analysis supports these results by identifying optic disc involvement and irradiation as a significant risk factor for optic neuropathy, but not the involvement of the macula and its received radiation dose as an impact factor on retinopathy. The basis risk of the development of radiation retinopathy was already very high, independent of any macular involvement, though if present it caused an even higher risk rise. The existence of macular edema in this study group did not correlate with irradiation dose on the macula. These results partly match and partly differ from those reported by Gragoudas et al. In their study on radiation vasculopathy in choroidal melanomas treated with

proton therapy, they too could detect a strong positive correlation of the dose applied to the optic disc and the resultant increased probability of developing a radiation optic neuropathy, though not as a linear relationship. The authors report a maximal tolerable dose of 30 CGE to the disc, with doses below this level being associated with only a minimal risk of optic neuropathy, whereas the present study showed that any radiation exposure above baseline can increase the probability for optic neuropathy, with the risk rising steadily and linearly [119]. A closer look at the anatomical conditions of the optic disc with regard to its blood supply might provide an explanation for the present study's results. The vascularization of the optic nerve head shows an interindividual variability consisting of posterior ciliary arteries, the central retinal artery and pial branches of different origin [143]. Moreover, Egbert et al. showed that the vascular changes, detectable via histopathology, that occurred in irradiated eyes were independent of the radiation dose delivered to the retina [99]. Based on these two findings, it is comprehensible that radiation delivered only to the disc margin and thus to the surrounding arteries possibly supplying the optic disc may already lead to optic neuropathy. Vascular damage and occlusion occurring after irradiation with small doses will thus result in optic neuropathy if the affected vessels are crucial to the optic nerve head supply. Accordingly, higher doses applied to these structures will increase the probability of a critical affection, thereby most likely accelerating and aggravating the development and extent of the clinical complication manifestation [144].

Concerning an increased likelihood of radiation maculopathy with increasing dose applied to the macula, Gragoudas and colleagues can again show a strong correlation, with the rate increasing linearly as a function of dose, though not as steeply as for optic neuropathy [119]. This study detected a significantly higher risk of radiation retinopathy with higher doses to the macula when compared with zero irradiation.

5.6 Visual outcome

In the present study, a significant difference in visual outcome was detectable, depending on whether the patient had developed a radiation-induced complication or not. Initial visual acuity was already quite low with a median of 0.3 logMAR (Snellen fraction 20/40), probably reflecting the high risk cohort consisting to a large number of patients with centrally located tumors deteriorating the vision. After proton beam radiotherapy, patients without manifestation of a radiation-induced posterior segment complication remained rather stable in their visual acuity, with the median level only worsening as much as down to 0.5 logMAR (Snellen fraction 20/60) at the last examination performed at a median of 25 months after proton therapy. A

significantly worse visual outcome however, could be observed in those patients who had been diagnosed with either radiation-induced retinopathy, optic neuropathy or both by the time of their last examination. Their median visual acuity was 1.3 logMAR (Snellen fraction 20/400) after a median of 52.1 months since PT. In a study on long-term visual outcome of 87 patients with diagnosed radiation retinopathy, Kinyoun et al. found similar though slightly better visual acuity results. They observed a median final visual acuity of 1.0 logMAR (Snellen fraction 20/200) in their study group, though already initial VA was better, with a median of 0 logMAR (20/20). But they report on radiation retinopathy only and with a closer look on the present study's results, which include results on radiation retinopathy solely as well, the visual acuity results observed in this subgroup match those of Kinyoun et al., with the median test result being 1.0 logMAR. Furthermore, Kinyoun and colleagues could detect a great difference in the final visual acuity of radiation retinopathy patients depending on the presence of a macula edema. Median VA of patients where macular edema was present and eyes with no macular edema was 20/200 (1.0 logMAR) and 20/30 (approximately 0.1 logMAR), respectively [107]. The present study, too, showed a worse and equally low median final visual acuity of 1.0 logMAR (20/200) if macular edema was present, though visual acuity in the radiation retinopathy patients without any macular edema was not as good as that reported by Kinyoun et al., though still slightly better, namely 0.9 logMAR (20/160). The authors only report on 87 patients in total, with only 21 of them having no signs of a macular edema. The patient group with data on macular edema this study reports on is twice as large, hence, the results may be more representative. In conclusion, these findings still agree with Kinyoun et al., indicating that in radiation retinopathy it is the presence of a macular edema that limits the patient's vision the most, though retinopathy affecting only the remaining retina already leads to a significant visual impairment. With a close look at the visual outcome in patients with appearance of radiation optic neuropathy, the present results furthermore suggest that it is in fact optic neuropathy that is associated with the most severe vision loss. Median final visual acuity in these patients was observed to be 1.5 logMAR (Snellen fraction 20/600) after a median of almost five years. These findings are consistent with the literature. Kim et al. report on parapapillary melanomas and find 5 year visual acuity to be even worse than "counting fingers" in more than 50% of the patients who developed optic neuropathy after proton beam therapy [126]. In another study of 147 patients with parapapillary choroidal melanomas treated with proton beam therapy, Riechardt and colleagues detect a visual acuity of 1.4 logMAR (20/500) 5 years after therapy. These numbers refer to the whole cohort, which produced 5 year rates of radiation retinopathy and optic neuropathy of 90.3% and 89.6%,

respectively. The authors also identify the radiation-induced optic neuropathy as the major reason for patients' visual loss after treatment with proton radiation [125].

Several other studies report on visual outcome after radiation therapy without attributing the visual impairment precisely to any radiation complication but in general to radiation retinopathy, optic neuropathy or secondary glaucoma as main effectors [120] and associating it with risk factors including retinal invasion by melanoma, close proximity to the optic disc or fovea and higher radiation doses delivered to both the disc and fovea, all factors correlated closely with the development of the complications in question, as seen in the foregoing [85, 106, 122, 145]. Development of radiation optic neuropathy is regarded as a major predictor for visual loss post-radiation next to radiation retinopathy but also retinal detachment and cataract, though there are more promising and accepted therapeutic options available for the treatment of the latter two complications [106, 146].

5.7 Conclusion

This study showed that radiation-induced retinopathy and optic neuropathy are heavily vision limiting complications occurring very frequently after proton beam radiation of choroidal melanomas with a latency varying from several months to several years. The main risk factors highly predictive for the development of these complications were identified to be above all a posterior tumor location, proximity to the fovea and optic disc and higher radiation doses to these two sensitive structures, especially for the manifestation of optic neuropathy. It could furthermore be detected, that even though both complications may result in strong visual impairment, the loss of visual function is most evident in radiation optic neuropathy. While first and foremost, local tumor control should in any case be ensured, the lack of true therapeutic options for optic neuropathy should encourage greater prudence in irradiating papilla-close melanomas. Knowing that the necessary shielding of the papilla will not often be realizable, it is important to inform the patient about his/her visual prognosis and incidence rate for radiation-induced optic neuropathy. There will be no alternative to adapting irradiation planning to minimize the risk of radiation retinopathy, since centrally located tumors always require central irradiation to ensure tumor control. But it might additionally be a valuable preventive strategy to then also treat those high risk patients with scatter laser or intravitreal injections prior to the appearance of any signs of radiation retinopathy or optic neuropathy, but further studies on these therapies' effectiveness in preventing these complications are needed.

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„Ich, Johanna Tillner, versichere an Eides statt durch meine eigenhändige Unterschrift, dass ich die vorgelegte Dissertation mit dem Thema: „Radiation Retinopathy and Optic Neuropathy after Proton Beam Therapy of Choroidal Melanoma – A Retrospective Analysis of the Incidence, Predictive Factors and Visual Outcome“ selbstständig und ohne nicht offengelegte Hilfe Dritter verfasst und keine anderen als die angegebenen Quellen und Hilfsmittel genutzt habe.
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Mein Lebenslauf wird aus datenschutzrechtlichen Gründen in der elektronischen Version meiner Arbeit nicht veröffentlicht.

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