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Iris and iridociliary melanoma : concepts in diagnosis and management

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Chapter **1**

General introduction

Aim of this thesis

The clinical distinction between benign iris naevi and malignant melanomas of the iris, as well as their management, has been a subject of controversy. This challenge is because of lack of clear-cut differentiating points between two on clinical examination and imaging. In addition many other iris lesions simulate iris melanoma. In the past few decades, considerable changes have been made in the diagnosis and management of iris melanomas due to the availability of new imaging techniques like ultrasound biomicroscopy (UBM) and anterior segment optical coherence tomography (AS-OCT) and new treatment modalities like plaque radiation therapy and proton beam radiotherapy. In addition, new iris implants have become available to treat the iris defects caused by iridectomy or iridocyclectomy.

The main aim of this thesis is to evaluate the clinical risk factors and imaging techniques for the diagnosis and to analyze the treatment outcomes of Ruthenium-106 plaque brachytherapy for iris and iridociliary melanomas in terms of tumor regression and its complications, survival and development of metastasis. This thesis also focuses on the differential diagnosis of iris melanomas. Understanding of these subjects can assist ophthalmologists in the diagnosis and evidence-based management of iris melanomas, therefore avoiding unnecessary treatment of an iris naevus.

Iris Melanoma - Epidemiology

Approximately 5% of all melanomas arise in ocular and adnexal structures[1]. Most of these (85%) are uveal in origin [2]. Uveal melanoma is the most common primary intraocular malignant tumor with an annual incidence of 6-8 per million population per year in Caucasians [3,4]. Uveal melanomas can be posterior, involving the choroid and/or posterior part of the ciliary body, or anterior. Anterior segment melanomas are divided into iris melanomas with and without anterior chamber angle extension and iridociliary melanomas which involve the iris and the anterior ciliary body. Iris and iridociliary melanomas account for 3-10% of all uveal melanomas and are the most common primary malignancy of the iris [5-7]. The iris naevi, important differential diagnosis of iris melanomas, are present in 4-6% of the population, whereas iris freckles can be seen in 60% of the population. The average age of patients with iris melanoma is between 40-50 years which is 10-20 years younger than in patients with posterior melanoma with an equal sex distribution [5,8-10]. Studies have demonstrated a statistically significant association between light

colored irides and the development of both iris naevi and melanomas but it does occasionally occur in African and Asians people [11,12]. Iris melanomas mostly originate in the peripupillary iris, followed by midzone and less frequently in the iris periphery and are located mostly in the inferior portion of the iris, more often temporally and peripherally [5,10,12-14]. Few epidemiological studies suggest the role of sunlight exposure in the pathogenesis of iris melanoma, but other reports showed either a weak positive or no correlation between sunlight exposure and development of uveal melanoma [4,15]. Metastatic spread of iris and iridociliary melanomas occurs by hematogenous dissemination. Metastasis is predominantly localized in the liver (87%) but can also involve the lung, bone and skin [16,17]. The rate of iris melanoma metastasis is lower than in posterior uveal melanomas and is reported to be 5% at 10 years and 10% at 20 years [18,19]. Risk factors for increased mortality are secondary glaucoma, anterior chamber angle involvement, extraocular extension and extension to the ciliary body [18].

Iris Melanoma – Diagnosis

Melanocytic lesions of the iris such as iris naevi and melanomas account for 49 - 72% of all iris tumors. Both are derived from neural crest cells and consist of benign or malignant proliferations of stromal melanocytes that replace the normal architecture of the iris stroma [8,9,20]. Iris freckles, on the other hand, consist of collection of melanocytes only superficially without stromal involvement. Whether iris melanoma arises de novo or from pre-existing lesions is unknown. It should be differentiated from the quite common iris naevi which are present in 4-6% of the population [21]. However, the clinical and histopathological distinction between benign iris naevi and malignant melanomas of the iris, as well as their management, is still controversial [5,13,22-29]. The younger age of iris melanoma patients at diagnosis also makes it more important to diagnose and treat them appropriately as their longer life expectancy makes them more prone to treatment complications.

The diagnosis of iris melanoma like the other uveal melanoma relies on a careful history, ocular examination and imaging.

History

Iris naevi and melanomas are usually asymptomatic and either present as a cosmetic blemish or are detected on routine examination. Advanced iris melanomas can cause cataract or secondary glaucoma with associated symptoms. In general, symptoms are present more often in patients with iris melanoma than those with iris naevus [21].

Questions regarding the history should include the time when the iris lesion was first noticed, whether there was any change in size or pigmentation, the presence of any complaints like visual disturbances or cosmetic problems. Patients should be asked to bring their past photographs at the next visit. These old photographs should be looked at to search for the presence of iris lesion.

Examination

Ocular examination for iris melanomas include complete ophthalmic examination with special attention to slit-lamp examination, taking the tumor measurements both longitudinally and transversely, IOP (intra-ocular pressure) measurement, 360° gonioscopy and transillumination. Direct, indirect and contact lens (including 3-mirror) ophthalmoscopy should be performed to examine center and periphery of the retina and to determine the posterior extension of an iris tumor. An examination of lens and ciliary body should be completed after pupillary dilatation. Photographic documentation is required to detect growth of the lesion over time.

An iris naevus is mostly a solitary, circumscribed tan to dark brown colored lesion located inferiorly. It can cause an irregular pupil, angle involvement and secondary cysts which were believed to be the signs of malignant transformation of an iris naevus. But now it is realized that an iris naevus can also cause these secondary changes [30].

Iris melanoma may be circumscribed or diffuse and present as pigmented or amelanotic mass. A circumscribed iris melanoma has a nodular shape, with irregular surface and can grow anteriorly into the anterior chamber angle or posteriorly to invade the ciliary body. It can also cause anterior chamber hemorrhage, secondary cataract, secondary glaucoma and/or corneal decompensation leading to oedema and band keratopathy [31,32]. A diffuse iris melanoma can develop in two ways. First mechanism is by primary infiltration of the iris stroma, causing iris thickening without any nodule formation [33]. The second way is by seeding of tumor cells from circumscribed iris or iridociliary melanoma [34]. Both mechanisms lead to acquired hyperchromic heterochromia with ipsilateral glaucoma. An iridociliary ring melanoma, is a variant of extensive iris and ciliary body lesion, involves over two thirds of the ciliary body circumference [35]. Ring melanoma of the anterior chamber angle is characterized by circumferential growth in the trabecular meshwork, resulting in secondary glaucoma, with relative sparing of iris and ciliary body [36]. Tapioca melanoma refers to an iris melanoma having lightly pigmented multifocal nodules, resembling frog eggs, that project into the anterior chamber and sometimes associated with glaucoma [37-39].

The clinical distinction between benign iris naevi and malignant melanomas

has traditionally been based upon size, increased vascularity, secondary cataract and documented growth. Clinical features favoring an iris melanoma are: prominent vessels on the surface of the tumor; elevated intraocular spread and anterior chamber seeding of tumor cells (Table 1) [5,7,8,10,28,40].

Table 1 Clinical features favoring an iris melanoma

Presence of symptoms
 Basal tumor diameter > 3mm
 Prominent tumor vascularity
 Pigment dispersion
 Elevated intraocular pressure
 Rapid growth

In a study by Jakobiec et al, 87% of the lesions diagnosed and surgically excised as iris melanomas by experienced clinicians were shown to be benign iris naevi on histopathology [24]. This has led to the need of a more precise identification of clinical factors and better imaging modalities to diagnose iris melanoma with more certainty. After Jakobiec, many studies focused on identifying tumor features that were significantly associated with melanoma and the rate of growth of suspected lesions. These include: a largest basal tumor diameter > 3mm; thickness >1mm; presence of pigment dispersion; prominent tumor vascularity; elevated intraocular pressure; tumor- related visual symptoms; secondary cataract; rapid growth and heterogeneous pigmentation [14,25,40-42]. Some features such as ectropion uveae, decreased iris motility and satellite lesions were not evaluated [42]. On the other hand, a few studies demonstrated an absence of specific clinical features correlated with the diagnosis and future enlargement of iris naevus or melanoma [24,29]. Therefore, the specific value of various clinical risk factors associated with diagnosis of iris melanoma remains unclear. In view of these facts the Dutch Oncological and Orbital Society felt a need for developing guidelines for the diagnosis of iris and iridociliary melanomas.

Differential Diagnosis

Cystic lesions, inflammatory processes, foreign bodies and benign and malignant neoplasms can simulate iris melanomas (Table 2) (Figure 1) [37,38]. This misdiagnosis of an iris lesion suspected of being a melanoma can lead to unnecessary ocular treatment. Ferry reported that 35% of enucleated eyes for

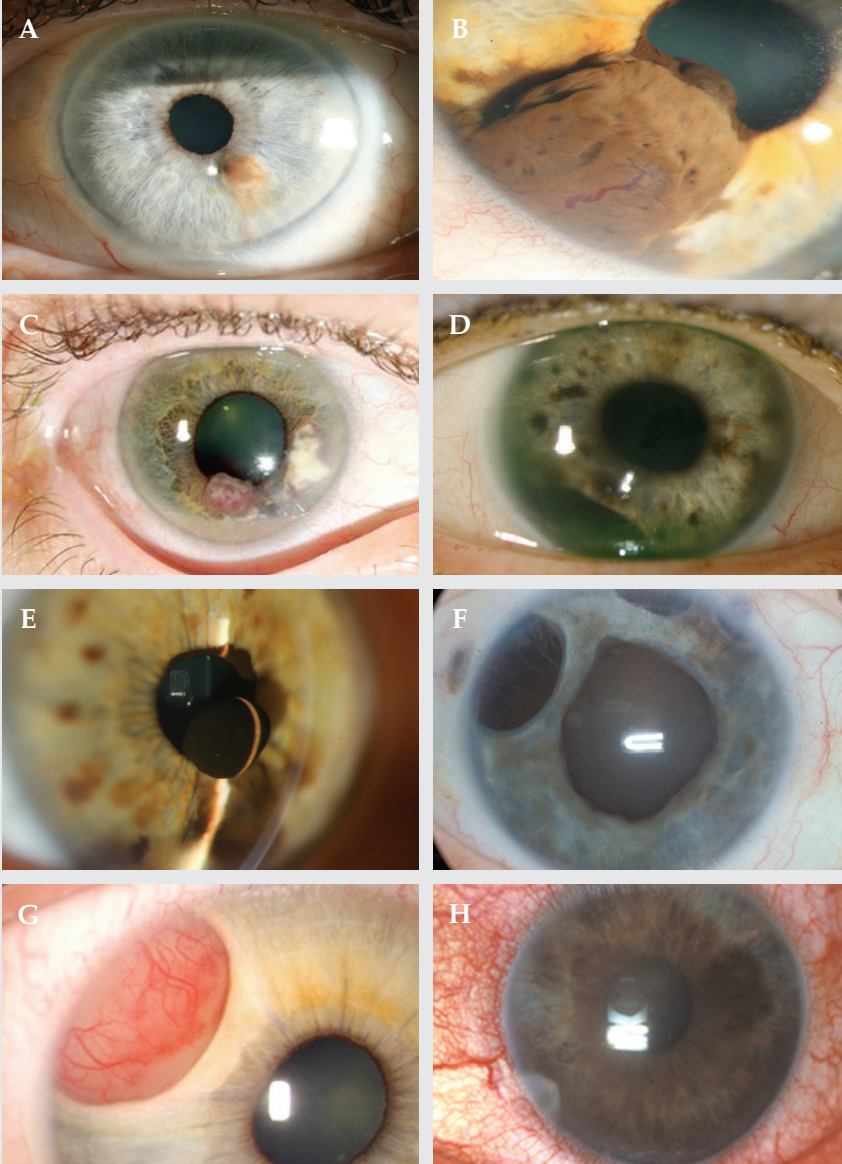
presumed iris melanoma contained simulating iris lesions [43]. Similarly a report by Shields showed that only 24% of lesions referred with a diagnosis of iris melanoma were correctly diagnosed. The most common simulating lesions found in this study were primary cysts (38%) and iris naevi (31%) [40].

Table 2 Differential diagnosis of iris and iridociliary melanoma according to pathogenesis

Neoplastic
<p><i>Benign</i></p> <ul style="list-style-type: none"> • Iris naevus • Iris pigment cyst • Lisch Nodules • Melanocytoma • Cogan-Reese syndrome • Bilateral diffuse melanocytic proliferation • Leiomyoma • Mesectodermal Leiomyoma • Lymphoid tumor • Adenoma of iris pigment epithelium <p><i>Malignant</i></p> <ul style="list-style-type: none"> • Iris metastasis (carcinoma/sarcoma) • Forward extension of posterior uveal melanoma involving the iris • Adenocarcinoma • Lymphoma • Leukemia
Inflammatory
<ul style="list-style-type: none"> • Granuloma • Sarcoidosis • Juvenile xanthogranuloma • Scleritis
Traumatic
<ul style="list-style-type: none"> • Foreign body • Implantation cyst • Iridocyclodialysis
Miscellaneous
<ul style="list-style-type: none"> • Essential iris atrophy • Heterochromia • Pigment dispersion syndrome • Amyloid

Figure 1 Differential diagnosis of iris melanoma:

A: Iris naevus B: Iris melanoma C: Iris metastasis D: Ciliary body melanoma extending to iris E: Iris cyst F: Cogan-Reese syndrome G: Iris leiomyoma H: Iris metastasis from skin melanoma

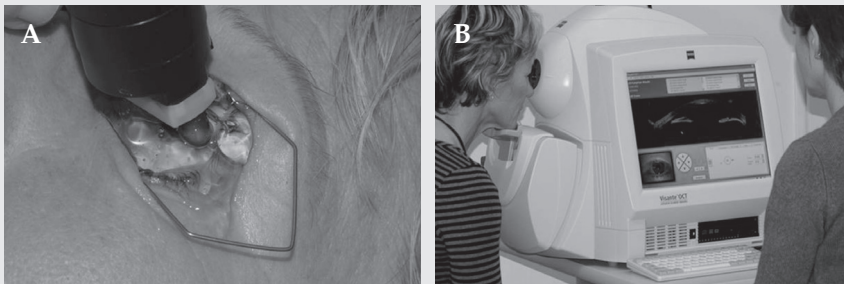


Investigations

Imaging of the iris melanoma included initially anterior segment fluorescein angiography and ultrasound examination. Fluorescein angiography is of little clinical help in differentiating between benign and malignant iris tumors, although various angiographic patterns have been defined in iris tumors. Iris naevi show distinct vascular network patterns or angiographic silence, whereas iris melanomas have irregular and indistinct vascular channels that fill later and show leakage (after 30 sec) [13,44-47].

The role of conventional ultrasonography (10MHz) in the diagnosis of choroidal melanoma is well established with a sensitivity of 93%, but for iris melanoma 10MHz ultrasonography does not provide sufficient information on structure and extension, because of its limited resolution of 300-400 μm , although it can provide some information regarding tumor size and dimensions [48-50]. Ultrasound biomicroscopy (UBM, 50 MHz), having a resolution of 20-50 μm with a tissue penetration up to 4mm, has dramatically improved imaging of iris and iridociliary tumors [50]. In the last decade, several studies have established a role for UBM in iris melanoma diagnosis especially excluding the presence or absence of ciliary body extension. Other parameters that have been studied are: nodular shape; basal tumor diameter; tumor thickness; internal reflectivity; secondary cysts and ciliary body involvement [51,52]. Reliable tissue typing with UBM has proved impossible so far, despite high resolution [53,54].

Figure 2 Examination procedure of **A:** UBM showing contact nature and supine position of patient, **B:** AS-OCT examination showing non-contact nature and sitting position of patient



Many other novel anterior segment imaging techniques have been developed during the last decade. These include Pentacam, Anterior segment optical coherence tomography (AS-OCT) and Slit-lamp optical coherence tomography. Pentacam, based on rotating Scheimpflug imaging, provides sharp and crisp images from the anterior corneal surface to the posterior crystalline lens. Optical coherence tomography is comparable to the ultrasound technique, but detects infrared light reflected from the tissues. AS-OCT works at 1310 nm wavelength with 4000 axial scans per second penetrating deeper through the highly-reflective sclera, and reducing the retinal exposure [55-57]. AS-OCT also facilitates frequent imaging because of its non-contact nature, so that it can be used to detect the tumor growth, which is a very important indication of malignancy. Slit-lamp OCT is an OCT machine adapted to work with a slit-lamp, so that while viewing the lesion with a slit-lamp, an OCT image can be taken. The main advantage of these techniques over UBM is their non-contact nature, thus avoiding the need for a skilled examiner and the complications of UBM like corneal erosion or oedema (Figure 2&3). Examples of UBM and AS-OCT images of iris naevus and melanoma are shown in figure 4,5&6.

Another imaging modality is magnetic resonance imaging (MRI), which can detect intraocular tumors and which distinguishes these from other ocular structures. Also, MRI has been shown to be more sensitive in detecting extra ocular extension than ultrasound or CT scan [58-60] (Figure 7). However, these MRI studies were performed with a 0.5 Tesla MRI.

Figure 3 Complications of UBM examination,
A: Corneal oedema, B: Corneal erosion (marked by arrow)

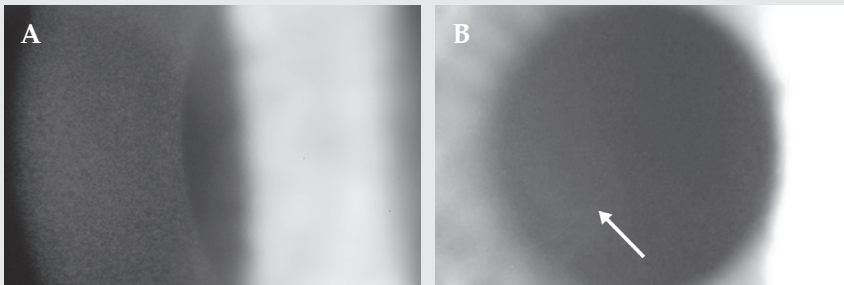


Figure 4 A: Iris naevus,
B: UBM image,
C: AS-OCT of the same
iris naevus

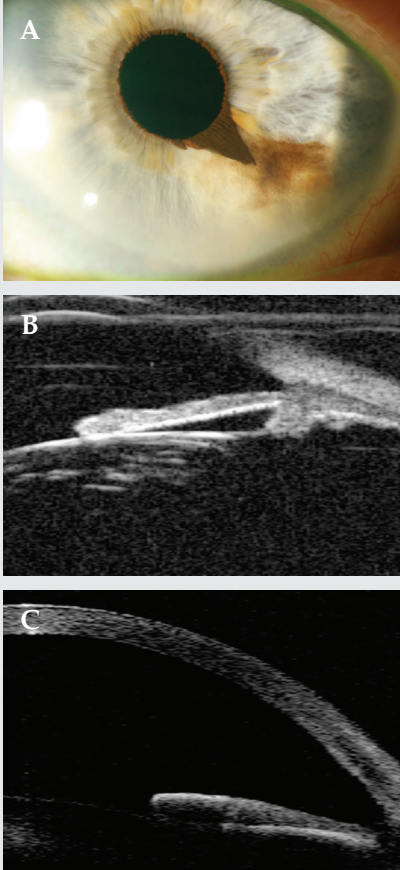
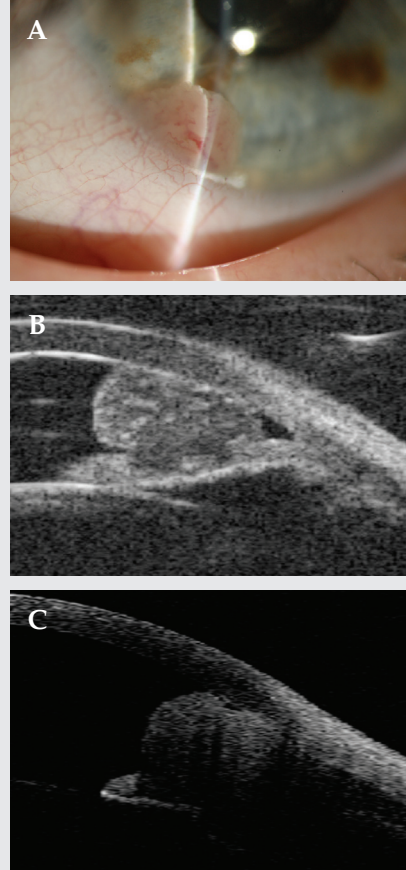


Figure 5 A: Iris melanoma,
B: UBM image,
C: AS-OCT of the same
iris melanoma



Fine needle aspiration biopsy (FNAB) or incisional biopsy is performed if there is diagnostic uncertainty despite other investigations. FNAB provides few cells but incisional biopsy provides more tissue although it is a difficult procedure.

Figure 6 A: Iris naevus in the upper nasal quadrant, B: UBM showing high reflectivity and intact posterior iris pigment epithelium

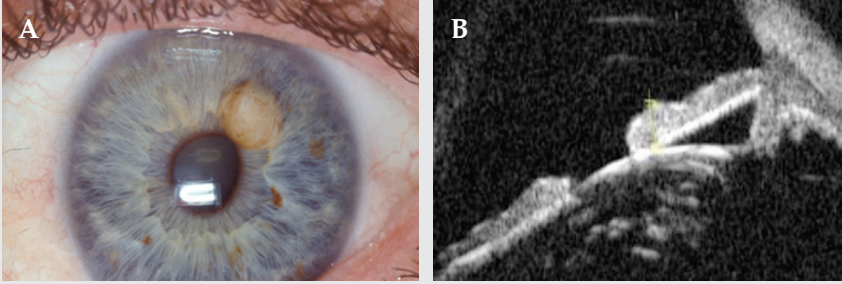
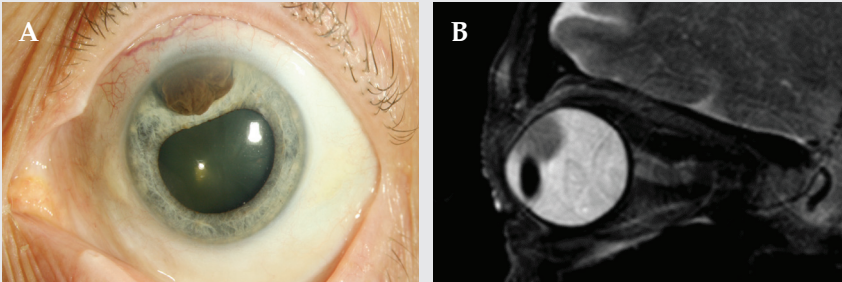


Figure 7 A: Iris melanoma clinical picture, B: Sagittal MRI T2 weighted image of the same patient shows an iridociliary tumor



In addition to confirm the diagnosis, these techniques can provide tissue for genetic testing. However, concerns have been raised for ocular tumor dissemination with these procedures [61,62].

Iris Melanoma - Treatment

Iris melanoma treatment has evolved towards a more conservative approach. For localized tumors, careful observation with photographic documentation is an accepted approach. The follow-up should be at every 3, 6, or 12 months depending on clinical circumstances [24,34,63].

Local Excision: iridectomy / iridocyclectomy

Surgical intervention may become necessary when the tumor shows growth and can be in the form of iridectomy / iridocyclectomy [25,63]. Complete excision by sector iridectomy is indicated when growth is more pronounced, the lesion involves the pupil and interferes with vision [29,63]. Iridocyclectomy is advised for peripheral tumors that are growing and involving the chamber angle and for peripheral tumors with associated glaucoma [34].

Complications of iridectomy include photophobia, glare, cataract, vitreous loss, hemorrhage and incomplete tumor excision. Cyclectomy may cause lens subluxation, cataract, hypotony, retinal detachment and phthisis. Moreover, manipulation of the tumor can theoretically cause malignant cells to disseminate thereby increasing the risk of local recurrence and metastasis [18,64]. Spherical optical aberrations can be a problem after iridectomy because of the increased pupillary size [65]. In addition, following iridocyclectomy for iridociliary tumors 50% of the patients had a poor vision (20/200 or worse) [66].

Enucleation

Enucleation is advised for large and diffuse iris melanomas, melanomas with angle seeding and secondary glaucoma and large ciliary body melanomas [67,68]. The quality of life is totally changed and enucleation is certainly associated with greater visual and psychological consequences for the patient. In this respect, the co-morbidity is high for surgical treatments of iris and iridociliary tumors in which 87% of the lesions diagnosed and treated as iris melanomas were shown to be benign on histology [24].

Plaque radiation therapy

In view of concerns about unnecessary treatment of benign iris naevi and its consequences, during the last two decades ophthalmologists have tried to develop more conservative treatments of iris melanomas to avoid the morbidity caused by excision and enucleation.

Plaque radiation therapy or brachytherapy refers to implantation of radioactive material close to tumor in the form of a plaque. The radioactive plaque emits

ionizing radiation, which is absorbed by tumor tissue. This causes DNA damage, loss of cell reproduction and even cell death. The absorbed dose is usually measured in Grays (Gy), with 1 Gray being equal to 1 Joule of energy absorbed by 1 kg of tissue.

Plaque brachytherapy was initially introduced for posterior uveal melanoma in the 1960s, and had until recently not been used for anterior uveal melanoma because of potential risks of radiation on the cornea and lens. It was started for iris melanomas in the 1990s and included Iodine (I-125), Palladium (Pd-103) and Ruthenium (Ru-106) plaques.

Iodine (I-125) emits low-energy photons in the 20-35 KeV range, resulting in a penetration of 10-15 mm tissue depth, having a half-life of 59 days. The first group of iris melanomas treated with iodine (I-125) plaque brachytherapy was reported in 1995 [69]. This treatment showed a good tumor control (93%) with few side effects. Later, more studies reported the use of I-125 for iris melanomas. The major radiation-related complications showed in these studies were cataract, glaucoma, and anterior uveitis [52,70].

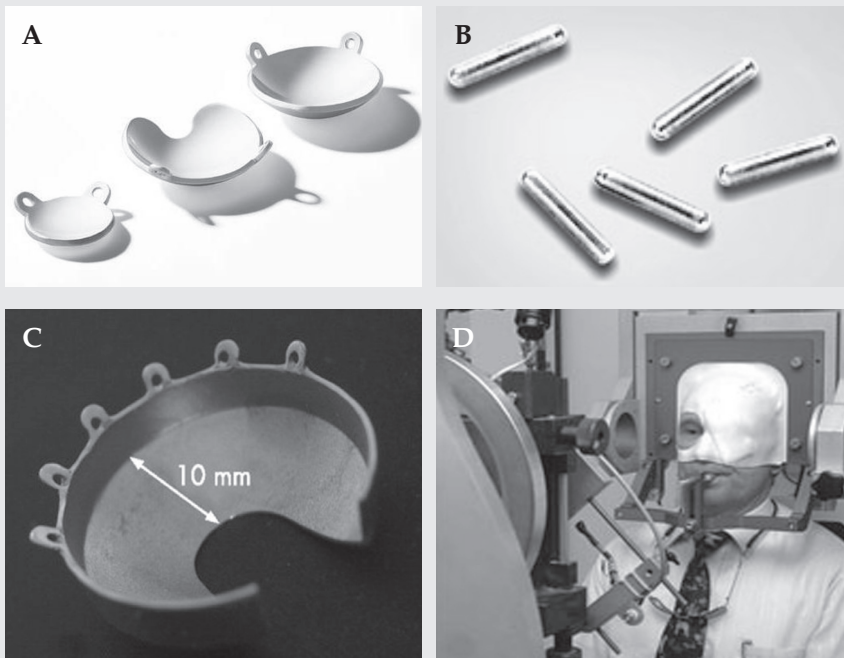
Palladium (Pd-103) generates low energy photons of 28 KeV, having a half-life of 17 days [71]. It has shown good tumor control for iris melanoma and the main side effect reported was cataract [72].

Ruthenium (Ru-106) emits a spectrum of beta-particles with a maximum energy of 3.5 MeV, resulting in a penetration of 5-6 mm tissue depth. Ru-106 plaque brachytherapy was first popularized by Lommatzsch for choroidal melanoma [73,74]. Later other reports also showed good tumor control and preservation of vision [75-80]. Because of its availability, Ru-106 has been used in Leiden for the treatment of choroidal melanomas since 1983 and for iris melanoma since 1997. The dose schedule initially used was a scleral dose of 800Gy for choroidal melanoma, 600 Gy for anterior ciliary body and 400 Gy for iris melanoma but this was recently changed to apex doses [79,81,82]. Therefore, a need was felt to develop a new model for calculating the radiation dose for iris and iridociliary melanomas taking into account the perpendicular tumor measurements. As yet, no study has defined the role of Ru-106 in the treatment of iris melanoma, in terms of local tumor control and side effects [82,83].

Proton beam radiotherapy, a form of external beam radiation, is also being used for iris melanoma treatment. It uses positively-charged protons with the energy of 65 MeV. The proton beam radiotherapy, with the properties of minimal scatter and deposition of most energy at the end of their range (Bragg peak), makes it

possible to deliver the maximum dose to the tumor with elimination of the dose proximal or distal to the tumor [84]. Studies using proton beam therapy for iris melanoma showed a high rate of local tumor control. The main complications reported were neovascular glaucoma, cataract and dry eyes [85,86]. Its use is limited because of its availability in only few centers worldwide. (Figure 6)

Figure 8 Different modes of radiation treatment for iris melanoma, **A:** Ruthenium-106 plaques, **B:** Iodine-125 seeds, **C:** Palladium-103 plaques, **D:** Proton beam radiotherapy



Outline of the thesis

The studies described in this thesis are intended to enhance the understanding of diagnosis, differential diagnosis, imaging and management of iris and iridociliary melanoma. This knowledge can help to treat the iris melanoma in a timely and effective manner to prevent metastasis, at the same time avoiding any unnecessary treatment of iris naevus.

Part I: Diagnosis of iris melanoma

Chapter 2 reviews the diagnostic features for iris melanoma and provides a 13 years prospective study of iris melanocytic tumors seen in Leiden, including the clinical risk factors and UBM characteristics and their significance with regards to therapeutic decisions. The role of anterior segment optical coherence tomography (AS-OCT) and other new anterior segment imaging techniques like Pentacam, SL-OCT were evaluated and compared with the established imaging technique of UBM in **Chapter 3**. **Chapter 4** focuses on the enhancement patterns seen with contrast on 3 Tesla MRI in differentiating iris simulating lesions from iris melanoma and showing the surgical technique of its removal.

Part II: Surgical management of iris melanoma and correlation with histopathology

Chapter 5 is a multicenter study, international, internet-based study to identify the clinical and pathologic characteristics of histology-proven malignant melanoma of the iris.

Chapter 6 focuses on the phakic iris implant used for eliminating the complications of iridectomy for iris melanoma and its results.

Part III: Plaque brachytherapy for iris melanoma

In the study described in **Chapter 7**, we evaluate the role of Ruthenium-106 plaque brachytherapy for iris and iridociliary melanoma in terms of tumor regression, survival and treatment complications during a 11 year-follow-up period.

More specific side effects of placing Ru-106 on the cornea for iris melanoma are evaluated in **Chapters 8 & 9**. This includes an analysis of the tear film and measurement of corneal endothelial cell density (ECD), accounting for dry eyes and endothelial cell loss respectively with a longer follow-up period.

In the summary and discussion (**Chapter 10**), the implications of the findings presented in this thesis are summarized and discussed.

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