Chapter 10

Summary and General Discussion
That the diagnosis and management of iris melanoma is challenging, is proven by the fact that most cases of melanocytic iris lesions that are diagnosed and surgically excised as iris melanomas were shown to be benign iris naevi [1]. Furthermore, local excision of iris tumors is associated with a high ocular morbidity and enucleation results in the loss of an eye [2,3]. Therefore, it is important to differentiate iris naevi from melanomas, thus avoiding unnecessary treatment of the iris naevi, while, on the other hand, early and effective treatment of iris melanomas is necessary because of concern about secondary local complications and metastasis.

Part I of this thesis concerns the diagnosis of iris and iridociliary melanomas according to clinical risk factors and ultrasound biomicroscopic (UBM) characteristics. The role of different new anterior segment imaging techniques in the diagnosis of these tumors was also evaluated. The focus of part II is the clinical and pathological characteristics of histologically-proven surgically-managed iris melanomas. It also deals with different surgical techniques to avoid the post-operative effects of iridectomy. Results of plaque brachytherapy with Ruthenium-106 in terms of tumor control and complications are investigated in part III.

Part I: Diagnosis of Iris melanoma

The diagnosis of iris melanoma relies on the presence of clinical risk factors and UBM characteristics. The clinical distinction between benign iris naevus and malignant melanoma has traditionally been based upon size, increased vascularity, secondary cataract and documented growth. Other clinical factors, that are significantly associated with melanoma and the future growth of suspected lesions, are: largest basal tumor diameter >3 mm, thickness >1 mm, presence of pigment dispersion, prominent tumor vascularity, elevated intraocular pressure, tumor-related visual symptoms, secondary cataract, rapid growth and heterogeneous pigmentation [4-8]. The advent of ultrasound biomicroscopy (UBM, 50 MHz) has dramatically improved the imaging of iris and iridociliary tumors [9,10]. In Chapter 2, the role of all of these factors is reviewed and the 14-year results of the use of an iris melanoma guidelines (Appendix 1&2), which has been used in our ocular oncology clinic, are shown. This guideline includes all the clinical risk factors and UBM characteristics associated with the diagnosis of iris and iridociliary melanoma. Initially, anterior segment fluorescein angiographic features were also included. However, as in general, UBM replaced anterior segment fluorescein angiography, these features were subsequently excluded from the guideline. We analysed this
guideline to know the most important clinical and UBM factors associated with the diagnosis of iris melanoma and observed that a clinical diagnosis of melanoma correlated with secondary cataract, diameter >3 mm, presence of symptoms, IOP >20 mmHg and age at onset >48 years. UBM characteristics correlating with diagnosis of melanoma were: thickness >1 mm; low reflectivity; basal diameter >3 mm; anterior chamber angle extension of tumor and presence of secondary cysts. The most important fact that we identified in our study was that ciliary body extension was not a significant factor in the multivariate model, in contrast with the belief that it is always a sign of malignancy. Therefore, we can emphasize that ciliary body extension may be a diagnostic factor for the diagnosis of melanoma but only in addition to the presence of other risk factors. Our study is the basis for modification of the current iris and iridociliary melanoma guidelines in which only the significant clinical risk factors and UBM characteristics are included, and we recommend the modified guideline as based on this study and attached as Appendix 3.

Although UBM characteristics were significantly associated with the diagnosis of iris and iridociliary melanoma, UBM is not readily available in all centers. Even in our hospital (LUMC, Leiden) it was not available till 2007 so the need was felt to evaluate other modes of anterior segment imaging for their usefulness in the diagnosis of iris melanoma. The advantage of these techniques over UBM is their non-contact nature, thus avoiding the complications of UBM [11-13]. In chapter 3, we evaluated the role of different imaging techniques like Pentacam, Anterior segment optical coherence tomography (AS-OCT) and Slit-lamp optical coherence tomography (SL-OCT) for diagnosis of iris naevus and melanoma and compared their results with the UBM. Our study showed that iris melanocytic tumors could be located by AS-OCT in 96% of the cases and the results were comparable to UBM images in 86% of patients. The main limitation of AS-OCT was its inability to visualize the ciliary body extension of tumors. SL-OCT and Pentacam were able to localize iris tumors in 67% and 18% of patients and were comparable to UBM in 10% and 0% of the patients, respectively. Therefore, Pentacam and SL-OCT are less reliable than AS-OCT and UBM for detecting and measuring anterior segment lesions. This study may encourage ophthalmologists to use AS-OCT for evaluation and frequent follow-up examination of iris tumors, but only for those not extending into the ciliary body. This may be helpful in the centers where UBM is not available and AS-OCT is present, usually because of its popularity in refractive surgery.

In Chapter 4, we focused on the use of Magnetic Resonance Imaging (MRI) for differentiating iris melanoma-simulating lesions, the most important of which is iris leiomyoma in young people, based on the enhancement patterns with contrast. 3 Tesla MRI of the case described, which was histologically proven to
be a leiomyoma, showed marked enhancement of the iris tumor on the T1-weighted image after gadolinium as compared to moderate enhancement in melanoma, confirming previous reports [14,15]. With the advent and availability of improved resolutions with 3 and 7 Tesla MRI, these MRI enhancement characteristics can gain more importance in the future.

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

Chapter 5 is a multicenter, international, internet-based study to identify the clinical, UBM and pathological characteristics of histology-proven melanoma of the iris. This is particularly important because there exists clinical difficulty in distinguishing iris melanomas from naevi and lack of major studies of histologically-confirmed iris melanomas after 1980s. We participated in this study with 34 patients from our center, who were treated for iris melanoma by excision, primary enucleation and secondary enucleation for recurrence after Ruthenium plaque therapy, between 1990 and 2010. This study identified that glaucoma was the most common presenting symptom and most iris melanomas were brown, unifocal, lacked heterogeneity, had a largest diameter of 5 mm and were found in the inferior iris (between the 3 and 9 o’clock meridians). Larger tumor size (>5 mm) was associated with the presence of intrinsic tumor vessels, more than 0.5 clock hours of angle involvement and the presence of an epithelioid and mixed cell type. The rate of metastasis from iris melanoma was found to be 10.7% at 5-year follow-up, which is quite high as compared to old reports [16].

Chapter 6 of this thesis deals with a technique developed to overcome the complications of local excision. The complications of iridectomy which are photophobia, glare and aberrations, can cause significant visual morbidity. We described the implantation of a customized phakic iris implant to reduce postoperative photophobia after sectorial iridectomy for iris melanoma. Follow-up of 8 years after this lens implantation has shown no complications. This surgical approach of iris melanoma should especially be used in young patients in whom the fear of radiation complications is high.

**Part III: Plaque brachytherapy for iris melanoma**

During the last two decades, ophthalmologists tried to develop more conservative treatments of iris melanoma to avoid the visually morbid effects of the conventional surgical managements. Radiation therapy in the form of plaque
irradiation started to be used for iris melanoma in the 1990s and included Iodine (I-125), Palladium (Pd-103) and Ruthenium (Ru-106) plaques [17-19]. Radiation for iris melanoma is also achieved by Proton beam radiotherapy [20,21]. Plaque brachytherapy with I-125 and Pd-103 and proton beam radiotherapy have shown good results but there was no study available regarding the use of Ru-106 for iris melanoma and its results, although it has been used in our center since 1997. In Chapter 7, we therefore determined the long-term effects of Ruthenium-106 plaque radiation therapy for iris and iridociliary melanomas in terms of tumor regression and complications. In this study, the tumors were classified by UBM imaging as iris melanoma if the tumor was confined to the iris and as iridociliary melanoma if the larger part of the tumor involved the iris with a small portion extending into the ciliary body.

A calculation model was developed for calculating the radiotherapy dosage, which takes into account different diameters of iris melanoma, is described in this chapter. During the surgical procedure before placement of the radioactive plaque, we used dummy plaques to ensure the exact localization, and included safety margins of 2 mm in all directions. We showed that Ruthenium plaque therapy is effective in the management of iris and iridociliary melanomas, with low recurrence rates (5%) and no severe ophthalmic complications. Anterior uveitis for only a few days developed in 14% as compared to 100% in an other study with I-125 [22]. This uveitis resolved in all patients with the use of topical steroids. Radiation-related glaucoma developed in one patient (3%) as compared to the rate of glaucoma in proton beam radiotherapy (53%), Iodine (33%) and Palladium (9%) [17,20-22]. This difference can be due to the fact that we do not offer Ru-106 for diffuse iris melanoma, as we perform enucleation in that case. The only significant complication was radiation-related cataract (36%), and progression of existing cataract (68%) which was treated with phacoemulsification.

One of our patients developed a recurrent tumor 180° away from the site of the original tumor; this was missed because of a focus at the follow-up examination on the site of the original tumor. Therefore, we recommend long term follow-up with 360° gonioscopy and UBM, in addition to routine clinical examination, which is of utmost importance to detect tumor progression or recurrence. When it was found in our study that Ruthenium-treated patients can develop cystoid macular edema (CME) after phacoemulsification, we started the use of prophylactic steroids around surgery. The regimen is 30 mg oral methylprednisolone starting 24 hours before surgery and continued daily for one week. Therefore this study will serve as a guideline for others for the treatment of iris melanoma patients with Ruthenium plaque therapy.
Apart from analyzing the Ru-106 tumor control effects and general complications, we evaluated this mode of treatment with regards to some specific complications. This included determination of the presence of dry eyes which has been reported to be very common after other radiation treatments [21,23]. The lacrimal gland region is not included in the field of irradiation in case of tumors treated with Ru-106, which constitutes an important difference in comparison with proton beam therapy or stereotactic radiation. We showed in Chapter 8 that dry eyes developed in only 2% of patients treated with Ruthenium plaque brachytherapy for iris and iridociliary melanoma. There was no significant difference in the tear film BUT and Schirmer test values of treated and untreated eyes (p-value: > 0.005), although the radiation source was in close proximity of the cornea. This close approximation of the radiation plaque could cause radiation damage directly to corneal epithelial cells leading to an unstable tear film or indirectly through damage to the limbal stem cells. Furthermore most of treated tumors were located inferiorly (60%) which can cause damage to goblet cells which have an increased density inferiorly.

In Chapter 9 we evaluated the effect of Ruthenium plaque radiation for iris and iridociliary melanoma on the corneal endothelium by determining the corneal endothelial cell density (ECD). This study was initiated by the fact that one young patient with iris melanoma, seven years after treatment with Ruthenium and later phacoemulsification for secondary cataract, developed corneal endothelial decompensation. The ECD in this patient showed a very low count in the affected eye and a normal count in the fellow eye. We searched the literature for the effect of different plaque radiation therapies like Iodine, Palladium and Proton on corneal endothelium but did not find any reports. Therefore, we determined the ECD to evaluate the cornea in patients with iris melanocytic lesions. The study was also relevant because we know that phacoemulsification affects the ECD [24] and because patients treated with plaque brachytherapy undergo phacoemulsification more often than the normal population. We found no significant differences between the two eyes in iris naevus, iris melanoma or iris melanoma treated with Ruthenium (p-value: >0.005). However, a significant difference between the eyes treated with Ruthenium that had undergone phacoemulsification and the non-treated fellow eyes was found (p=<0.001). This difference remained significant (p= value: <0.001) after adjusting the ECD for phacoemulsification-related loss. Therefore corneal endothelial cell density seems to be significantly reduced by phacoemulsification for secondary cataract in iris melanoma eyes treated with Ruthenium plaque therapy.
Conclusions and future perspective

This thesis describes various concepts for a better understanding of diagnosis, differential diagnosis, imaging and management of iris and iridociliary melanomas which are generated from cases treated over the span of 14 years (1997 – 2010). After analysing which clinical risk factors and UBM characteristics were significantly associated with the diagnosis of iris and iridociliary melanoma, we created a modified iris and iridociliary melanoma guidelines. This guideline (Appendix 3) can be used in general and ocular oncology clinics to differentiate between an iris naevus and a melanoma and hence indicate their appropriate management. However, we recommend a re-analysis of this new guideline after a few years.

While we show that AS-OCT can be used to evaluate the progress of suspected iris melanoma (provided that the lesion does not extend into the ciliary body), and show different reflectivity patterns, our findings are based on the experience with light colored irides; brown eyes can produce different reflectivity patterns which indeed was observed in two of our cases. Further research is needed to elaborate on and confirm our findings. Advancements in the resolution of MRI can give important diagnostic clues in differentiating iris melanoma from other simulating lesions especially in young people, as shown in our case of iris leiomyoma. Precise tumor measurements of iris melanoma are also becoming more important with the availability of Proton beam radiotherapy in The Netherlands in the near future. This treatment modality delivers the maximum dose of irradiation over the calculated area only while delivering almost negligible radiation on the surrounding areas. For this goal, studies are needed that explore the potential of the high resolution 3 and 7 Tesla MRI in getting the accurate measurements of iris and iridociliary melanoma.

The metastatic rate of iris melanoma is 10.7% at 5-years in the multi-center study presented in this thesis. Therefore, iris melanoma should be treated appropriately as soon as possible to avoid metastasis. The participation in studies that include patients from all parts of the world must be stimulated in all fields of ocular oncology in order to include large enough numbers of patients to develop general guidelines. Therefore this multi-center study can serve as a basic framework for upcoming studies.

Our study shows that Ruthenium plaque brachytherapy is effective in the management of iris melanoma and provides good tumor control. We introduced a calculation model for radiotherapy dosage that takes into account different diameters of iris melanoma. Regular and long term follow-up is needed in these patients with 360° gonioscopy and UBM for detecting tumor recurrence. We recommend the follow-up interval in the initial period after plaque brachytherapy...
to be 3 months during the first year and than every 6 months for another 2 years, followed by yearly examinations, depending on the tumor regression and associated complications. Our study for estimating the corneal ECD in Ruthenium-treated patients for iris melanoma identified many patients with low ECD after undergoing phacoemulsification for secondary cataract by experienced surgeons. We recommend further study to follow ECD in these patients to know the progress of endothelial cell loss and associated complications. Such data will provide the time frame of symptoms and signs of endothelial loss in these patients and can help to predict this loss in future patients and to schedule their follow-up accordingly.

With this thesis we have helped to unfold some mysteries associated with the diagnosis and management of iris and iridociliary melanoma, which may help others working with these tumors to differentiate between benign and malignant tumors and to provide proper care to patients with this complicated disease.
References
