Stereotactic radiotherapy of uveal melanoma: The Dunedin experience

Genevieve Frances Oliver (BHB, MBChB, PGDipOphthBS)

A thesis submitted for the degree of
Master of Ophthalmology
At the University of Otago, Dunedin, New Zealand
September 2015
Abstract

Uveal melanoma is a rare disease causing significant mortality. Metastatic disease - for which there is no treatment - often occurs before the primary tumour is diagnosed. In addition to enucleation, there are many globe-sparing ways of treating the primary tumour. Fractionated stereotactic radiotherapy is one such treatment, delivering a homogenous dose of radiation to the tumour and allowing normal tissue the chance to recover between fractions.

The aim of this thesis was to evaluate the effectiveness of fractionated stereotactic radiotherapy for the treatment of uveal melanoma in the New Zealand population. The main outcome measurements were local tumour control, visual acuity, radiogenic side effects and metastatic death.

A retrospective audit of clinical notes was performed on all patients with uveal melanoma treated with fractionated stereotactic radiotherapy in Dunedin, New Zealand, from July 2001 to December 2007. All twenty-seven patients treated during this period were included.

Local control was achieved in all patients. Three patients required secondary enucleation for intractable pain, recurrent vitreous cavity haemorrhage, and recurrent retinal detachment. Visual acuity deteriorated in eighteen of the remaining twenty-four patients (75%), and mean Snellen acuity dropped from 6/6 at baseline to 6/21 at final follow-up. Eight patients developed radiation retinopathy, one patient
developed optic neuropathy, and two patients developed neovascular glaucoma. At final follow-up, three patients were known to have died of metastatic disease.

Fractionated stereotactic radiotherapy is an eye-sparing treatment option for patients with uveal melanoma. Data from this study supports international literature that this is a useful addition to the treatment armamentarium for this cancer.
I would like to thank my supervisors Dr Lyndell Kelly and Professor ACB Molteno. I acknowledge the OSNZ Postgraduate Education Trust Fund for their financial support. I thank my family and friends for their unfailing encouragement, especially Thérèse Oliver for her patience and technical support, and Anne-Marie Yardley.

To Mrs Tui Bevin, research fellow, proof-reader and voice of reason: thank you, thank you, thank you.
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<th>Description</th>
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<tbody>
<tr>
<td>ALT</td>
<td>Alanine transaminase</td>
</tr>
<tr>
<td>ARMD</td>
<td>Age-related macular degeneration</td>
</tr>
<tr>
<td>AST</td>
<td>Aspartate aminotransferase</td>
</tr>
<tr>
<td>BAP1</td>
<td>BRCA1-associated protein 1 tumour suppressor gene</td>
</tr>
<tr>
<td>BRCA1</td>
<td>Breast cancer 1 gene</td>
</tr>
<tr>
<td>BRVO</td>
<td>Branch retinal vein occlusion</td>
</tr>
<tr>
<td>COMS</td>
<td>Collaborative Ocular Melanoma Study</td>
</tr>
<tr>
<td>DNA</td>
<td>Deoxyribonucleic acid</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
</tr>
<tr>
<td>FDG</td>
<td>Fluorodeoxyglucose</td>
</tr>
<tr>
<td>FFA</td>
<td>Fundus fluorescein angiography</td>
</tr>
<tr>
<td>FNAB</td>
<td>Fine-needle aspiration biopsy</td>
</tr>
<tr>
<td>GGT</td>
<td>Gamma-glutamyl transpeptidase</td>
</tr>
<tr>
<td>GTC</td>
<td>Gill-Thomas-Cosman</td>
</tr>
<tr>
<td>Gy</td>
<td>Gray</td>
</tr>
<tr>
<td>HIF-1α</td>
<td>Hypoxia-inducible factor 1 alpha</td>
</tr>
<tr>
<td>LDH</td>
<td>Lactate dehydrogenase</td>
</tr>
<tr>
<td>logMAR</td>
<td>Logarithm of the minimum angle of resolution</td>
</tr>
<tr>
<td>MeV</td>
<td>Mega-electronvolt</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic resonance imaging</td>
</tr>
<tr>
<td>NF-1</td>
<td>Neurofibromatosis type one</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
</tr>
<tr>
<td>--------------</td>
<td>--------------------------------------------------</td>
</tr>
<tr>
<td>PET</td>
<td>Positron emission tomography</td>
</tr>
<tr>
<td>RNA</td>
<td>Ribonucleic acid</td>
</tr>
<tr>
<td>SD-OCT</td>
<td>Spectral domain-optical coherence tomography</td>
</tr>
<tr>
<td>SRS</td>
<td>Stereotactic radiosurgery</td>
</tr>
<tr>
<td>SRT</td>
<td>Stereotactic radiotherapy</td>
</tr>
<tr>
<td>TNM</td>
<td>Tumour, Node, Metastasis cancer staging</td>
</tr>
<tr>
<td>TTT</td>
<td>Transpupillary thermal therapy</td>
</tr>
<tr>
<td>VEGF</td>
<td>Vascular endothelial growth factor</td>
</tr>
<tr>
<td>VEGF-A</td>
<td>Vascular endothelial growth factor subtype A</td>
</tr>
<tr>
<td>VEGFR</td>
<td>Vascular endothelial growth factor receptor</td>
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</table>
CHAPTER 1
Introduction

1.1 Background

Uveal melanoma is a rare disease causing considerable morbidity and mortality. While research over the last fifty years has led to significant improvements in life expectancy for cutaneous melanoma, there has been very little improvement in the prognosis of uveal melanoma. As long as local control is achieved, there is no evidence to suggest superiority of any particular treatment of the primary uveal tumour. Success in treating metastatic disease is disappointing, and given the low incidence of this cancer, it is difficult to conduct randomized controlled trials and provide a strong evidence base to guide treatment management.

1.2 Aim

The aim of this thesis was to review the pathophysiology and management of uveal melanoma and detail in particular the first cohort of patients with uveal melanoma who underwent stereotactic radiotherapy in Dunedin, New Zealand, from July 2001 to December 2007. There have been a number of case series around the world with small data sets and this study will contribute to the current body of knowledge.
1.3  Chapter outlines

The second chapter will describe the pathophysiology and cytogenetics of uveal melanoma. Chapter three will present the clinical features and associations of uveal melanoma. The following chapter will outline surgical treatment options. Chapter five will detail the principles of radiotherapy and its application in the treatment of uveal melanoma. Results, methods and discussion are presented in the six, seventh and final chapters.

1.4  Nomenclature

For the purposes of this thesis, the term uveal melanoma refers to ciliary body and choroidal melanoma. Iris melanoma is considered to be a different entity with different pathophysiology and prognosis.
2.1 Anatomy of the uveal tract

The uveal tract is the middle vascular layer of the eye, and consists of the iris, ciliary body and choroid (see Figure 2.1). It is dark brown in colour and its name is derived from its resemblance to a grape (Latin, *uva*) when exposed after removal of the sclera. The uveal tract is derived embryologically from vascular channels, neural crest cells and neuroectoderm. The iris is located anterior to the crystalline lens, forming the boundary between the anterior and posterior chambers of the eye, and controls the amount of light transmitted through the pupil, its circular aperture. The number and size of melanin pigment granules present in the anterior stromal melanocytes determine iris colour. The posterior portion of the iris is lined with a double-layered pigment epithelium arranged in an apex-to-apex configuration.

The ciliary body extends from the iris root posteriorly to become continuous with the choroid at the ora serrata. The inner portion of the ciliary body is lined with a double layer of epithelial cells, the outer layer being pigmented. These cells are involved in the production of aqueous humour. Ciliary processes extend inwards to join the zonules, attached to the crystalline lens. The ciliary muscle contracts during accommodation, a process that increases the dioptric power of the lens. The choroid is the pigmented vascular tissue forming the middle layer of the posterior part of the eye. It lies between Bruch’s membrane – external to the retinal pigment epithelium -
and the sclera, extending from the ora serrata anteriorly to the optic nerve posteriorly. Its main function is to provide oxygen to the outer avascular retina.

**Figure 2.1: Anatomy of the eye. From Netter's Clinical Anatomy**

Melanocytes are melanin-producing cells of neural crest origin. They are present in the skin, eyes, inner ear, and meninges, and their function in humans includes photoprotection, trapping reactive oxygen species, sequestering metal ions, and
binding certain drugs and organic chemicals. Melanin is a biopolymer stored in specialized vesicles called melanosomes. Human melanocytes synthesize two distinct types of melanin, both of which are present in uveal melanocytes. Melanogenesis was thought to only occur during fetal development but evidence is emerging in support of the hypothesis that melanogenesis does occur in the adult eye. This has been demonstrated by the hyperpigmentary side effects with use of prostaglandin analogues in the treatment of glaucoma.

2.2 Tumour biology

A neoplasm is an unregulated proliferation of cells. Neoplasia arises from non-lethal genetic damage causing clonal expansion of a single progenitor cell. Malignant neoplasms invade contiguous tissues and metastasize to distant sites. A melanoma is a malignant proliferation of melanocytes. Choroidal melanoma is the most common type of uveal melanoma (90%), followed by ciliary body (7%) and iris melanoma (3%).

Angiogenesis, or new vessel formation, is a requirement for the continued growth of primary and metastatic cancers. For a tumour to increase in size above a few thousand cells (about 1-2 mm$^3$) it needs a new vascular supply. Uveal melanoma is a highly vascular tumour, and high microvascular density correlates with worse survival. Tumour angiogenesis is a complex process involving the degradation of extracellular matrix, migration and proliferation of post-capillary venule endothelial cells and tube formation. Many tumours secrete polypeptides and platelet-derived growth factors that initiate and regulate the process of angiogenesis. Multiple factors exist that can stimulate an angiogenic response, and targets include endothelial cells and inflammatory cells to promote vessel formation. The most important angiogenic
factors are thought to be VEGF (vascular endothelial growth factor) and basic fibroblast growth factor.\textsuperscript{11} Other factors play an important role, including angiogenic inhibitors, adhesion molecules, matrix metalloproteinases and plasmin.

### 2.3 Cytophysiology

Carcinogenesis, or cancer formation, is a multistep process at phenotypic and genetic levels resulting from the accumulation of mutations. Six essential alterations in cell physiology, universal to all cancers, collectively dictate malignant growth:\textsuperscript{12} self-sufficiency in growth signals; insensitivity to growth inhibition signals; evasion of apoptosis; limitless replicative potential; sustained angiogenesis; and tissue invasion and metastasis. This transformation is a multi-stage process that occurs over a period of years. It is estimated that a minimum of four mutated genes are required for the transformation of a normal cell into a malignant phenotype.\textsuperscript{11} Several groups have demonstrated that these ‘hallmarks of cancer’ can be applied to uveal melanoma pathogenesis, and that genetic and epigenetic events in the development and dissemination of uveal melanoma enable malignant uveal melanocytes to proliferate and survive autonomously.\textsuperscript{13}

Cancer may be caused by a chance mutation, or chemical substances, infectious agents, radiation or inherited genes. These cause mutations in genes that regulate cell growth, death and repair. The unregulated growth of cancer cells results from the sequential acquisition of somatic mutations in four kinds of normal regulatory genes:

1. **Proto-oncogenes** are normal genes that promote cell growth and are ubiquitous in normal cells. These genes become oncogenes as a result of mutation, driving the malignant transformation of normal cells into cancerous cells and promoting
uninhibited cellular proliferation. Mutation of a single allele leads to gain-of-
function and cellular transformation; thus they are referred to as dominant
mutations.

2. The mutation of genes involved in **apoptosis** causes cell division even in the
presence of DNA damage.

3. **DNA mismatch repair genes** normally maintain the integrity of the genome and
DNA replication, with inactivation allowing the successive accumulation of
further mutations.

4. **Tumour suppressor genes** are also present in normal cells. Their function is to
inhibit cellular proliferation. Mutation causes loss-of-function and the inhibitory
activities of tumour suppressor genes are inactivated, permitting unregulated cell
growth.

Epigenetics refers to the molecular mechanisms resulting in reversible and heritable
changes in gene expression beyond those caused by alterations in DNA sequence.
These mechanisms ultimately determine which genes are expressed and which are
kept silent, and largely account for phenotypic variation between individuals with
identical genotypes. Principal epigenetic mechanisms include DNA methylation,
histone modification, and non-coding RNA regulation.\(^\text{14}\) These mechanisms are also
likely to contribute to the development and function of self-renewing ‘cancer stem
cells’.

Since the early 1980s, karyotype analyses of uveal melanoma have found an
association with alterations of chromosomes 3, 6 and 8,\(^\text{15-18}\) linking them to metastatic
death.\(^\text{19-22}\) Common genetic changes are loss of 3p and 6q and gain of 6p and 8q.\(^\text{23-25}\)
The most common karyotypic abnormality in uveal melanoma is monosomy 3, with
the loss of an entire chromosome. The consistent loss of such a large chromosome has
never been reported for any other tumour type.\textsuperscript{26} The frequent loss of a specific chromosome is thought to represent one step in the inactivation of a tumour suppressor gene residing on the lost chromosome.\textsuperscript{27} Inactivation of the second gene could result from a deletion, point mutation or the inhibition of its expression due to epigenetic mechanisms.

Monosomy 3 is associated with aggressive tumour behaviour. Prescher et al in 1996 reported a three-year relapse-free survival rate of 50\% in patients with monosomy 3, compared to 100\% in patients whose tumours retained both chromosomes.\textsuperscript{20} They also found that metastasis in the absence of monosomy 3 is extremely rare, which has been confirmed by others.\textsuperscript{19, 20, 28} Scholes found that monosomy 3 also correlates with a poor prognosis after treatment, noting its greater association with metastatic disease than the presence of other tumour features such as epithelioid histology, PAS+ loops, ciliary body involvement, or large basal tumour diameter.\textsuperscript{28} The high frequency of monosomy 3 may indicate that there is a suppressor locus for uveal melanoma on this chromosome. However, simple determination of monosomy 3 is challenging as the chromosomal defect can be masked by (1) a cryptic or partial deletion;\textsuperscript{29} (2) acquired homozygosity (isodisomy) with duplication of chromosome 3 from the same parent chromosome, or (3) modulation by other chromosomal errors, such as 6p or 8q gain.\textsuperscript{30}

Other frequently observed abnormalities involve chromosomes 6 and 8. Abnormalities in chromosomes 3 and 8 tend to occur together, with multiplication of 8q,\textsuperscript{26, 31, 32} and have a poor outcome.\textsuperscript{21} Chromosome 8 abnormalities are associated with large tumour size and aggressive histology.\textsuperscript{25} Trisomy 8, duplication of 8q or isochromosome 8 occurs frequently and has been found in 50-60\% of enucleated tumours.\textsuperscript{33} Chromosome 8q gains show a highly significant association with reduced
survival probability\textsuperscript{19} and represent an important but later stage in tumour progression.\textsuperscript{33} Chromosome 6 abnormalities consist mainly of gains of 6p or deletions of 6q.\textsuperscript{33} In 1988, Griffin et al was first to describe trisomy of 6p as a cytogenetic anomaly in uveal melanoma.\textsuperscript{17} Multiplications of 6p appear to be associated with a good prognosis.\textsuperscript{32}

Gene expression profiling analyses tumour RNA and is a more reliable method of detecting mutations in tumours than karyotyping. This method has been independently validated and has identified two distinct molecular classes of uveal melanoma that strongly predict metastatic death. These were previously unrecognized because they are not obviously distinguishable by clinicopathological features. Class one tumours are low-grade and have disomy 3.\textsuperscript{34} Class two tumours are associated with liver metastases and a poor prognosis, displaying global down-regulation of neural crest genes and melanocyte-specific genes on chromosome 3. The class two gene expression profile correlates with mutations in the BRCA1-associated protein 1 (BAP1) tumour suppressor gene located on chromosome 3, which is commonly lost in uveal melanoma.\textsuperscript{35}

In uveal melanoma with poor prognosis, there is a general dysregulation of epigenetic modifiers. A recent study comparing disomy (class 1) and monosomy 3 tumour cells (class 2) found transcriptional downregulation of genes encoding epigenetic regulatory enzymes in association with monosomy 3.\textsuperscript{36} A number of signalling pathways are known to be disrupted in uveal melanoma.

In most uveal melanomas, the retinoblastoma and p53 pathways are functionally inhibited, although the tumour suppressor genes themselves are rarely mutated.\textsuperscript{13, 37} These pathways are inhibited via epigenetic mechanisms and usually as a result of
cyclin D1 (in the retinoblastoma pathway) and MDM2 overexpression (in the p53 pathway). PTEN inactivation is also implicated in the progression of uveal melanoma. The mitogen-activated protein kinase/extracellular signal-related kinase pathway is essential for mediating cell-cycle progression and is activated in uveal melanoma but mutations in candidate oncogenes have not yet been identified.\(^{38}\) Tumours may also result from the amplification or mutation of an oncogene. It has been found that 46% of uveal melanoma and 83% of blue naevi carry mutations in the GNAQ gene, a Gq protein alpha subunit.\(^{39}\)

### 2.4 Tumour classification

The first classification for ciliary body and choroidal melanoma was published in 1868 in Heidelberg, Germany, by Knapp (1839-1911).\(^{40}\) Knapp divided tumours into four stages, according to the presence and absence of symptoms, extraocular extension, and distant metastasis. In 1931, Colonel George Callender at the Armed Forces Institute of Pathology reported on a series of 111 eyes studied histologically.\(^{41}\) He found several easily distinguished histological types: spindle-shaped cells, epithelioid cells and fascicular cells. Spindle cell tumours are composed of sheets, whorls, and irregular arrangements of spindle-shaped cells, with long, oval nuclei. He separated them into two divisions. The spindle A cells lack distinct nucleoli and have fine chromatin, whereas spindle B cells have more prominent nucleoli and coarse chromatin. Epithelioid tumours have a distinct histological appearance similar to a fried egg with a large nucleus and small distinct nucleoli. Fascicular tumours contain cells that radiate about the centre of a column in a palisade arrangement, with an oval nucleus and distinct nucleolus.
Callender found that epithelioid cells appear the most malignant, with numerous mitotic figures. Patients with tumours consisting of spindle cells unmixed with other types have a more favourable outlook that those with epithelioid, fascicular or mixed types. Large nucleoli and high numbers of mitotic figures are associated with a high risk of metastasis. Increased pigmentation, macrophage and lymphocyte infiltration are also associated with increased metastasis.

In 1986 The Collaborative Ocular Melanoma Study (COMS) standardized size definitions of small, medium and large choroidal melanomas in more than forty North American centres. The COMS size distinctions have since been used in many studies (Table 2.1):

<table>
<thead>
<tr>
<th>Table 2.1: COMS tumour size</th>
</tr>
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<tbody>
<tr>
<td>Small</td>
</tr>
<tr>
<td>Tumour height (mm)</td>
</tr>
<tr>
<td>Largest basal diameter (mm)</td>
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</table>

The seventh edition of the Tumour, Node, Metastasis, classification (TNM7) became effective in 2010 and is based on the extent of the primary tumour and the presence of any metastases. Size boundaries are based on the COMS classification, also taking into account ciliary body involvement and extraocular spread (Figure 2.2). Risk of metastatic death is based on a group of 7,369 patients analyzed by the European Ophthalmic Oncology Group and is estimated according to ocular tumor stage (with
categories having the same prognosis grouped into the same stage); regional lymph node involvement; and the presence of known metastases. Based on anatomic classification, the ten-year Kaplan-Meier estimate of survival for T1 tumours is 89% (Figure 2.3).51

![Figure 2.2 (above): TNM tumour size](image)

![Table 2.2 (below): Overview of the classification of malignant ciliary body and choroidal melanoma in the seventh edition of the TNM classification](image)

<table>
<thead>
<tr>
<th>Tumour extension outside the choroid</th>
<th>Size category, see Figure 2.1</th>
<th>None</th>
<th>Ciliary body only</th>
<th>Extraocular only, ≤5 mm</th>
<th>Ciliary body and extraocular ≤5 mm</th>
<th>Any extraocular &gt;5 mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>T1a (stage I)</td>
<td>T1b (stage IIA)</td>
<td>T1c (stage IIA)</td>
<td>T1d (stage IIA)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T2</td>
<td>T2a (stage IIA)</td>
<td>T2b (stage IIIB)</td>
<td>T2c (stage IIIA)</td>
<td>T2d (stage IIIA)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T3</td>
<td>T3a (stage IIIB)</td>
<td>T3b (stage IIIIA)</td>
<td>T3c (stage IIIA)</td>
<td>T3d (stage IIIIB)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T4</td>
<td>T4a (stage IIIIA)</td>
<td>T4b (stage IIIB)</td>
<td>T4c (stage IIIIB)</td>
<td>T4d (stage IIIC)</td>
<td>T4e (stage IIIC)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: TNM, tumour, node, metastasis
Clinical and pathological classifications are identical; if N1 or M1, the stage is IV regardless of size category.
2.5 Metastasis

Invasion and metastasis are properties unique to cancer cells and lead to the direct extension of the tumour outside its tissue of origin. Metastasis refers to the transfer of malignant cells from one site to another not directly connected with it.\textsuperscript{11} The first account of metastases from an ocular melanoma was described in the eighteenth century in the artist Sir Joshua Reynolds (1723-1792), who died at the age of sixty-seven, eighteen months after losing vision in his left eye.\textsuperscript{52} Circulating tumour cells penetrate capillaries and venules to invade distant sites. Lymphatic spread is also common, however the eye has no lymphatic drainage and uveal melanomas metastasise via haematogenous spread, usually to the liver. A number of steps are required for malignant cells to establish a metastasis:\textsuperscript{11}
- Invasion of the basement membrane underlying the tumour
- Movement through the extracellular matrix
- Penetration of vascular (or lymphatic) channels
- Survival and cell cycle arrest within the circulating blood or lymph
- Exit from the circulation into a new tissue site
- Survival and growth as a metastasis, a process that involves angiogenesis

Calculation of melanoma doubling time suggests that most uveal melanoma metastases are initiated up to five years before diagnosis and primary treatment.\textsuperscript{53} Hepatic metastases occur early in the development of uveal melanoma at a time when the primary tumour may be too small to be detected clinically.\textsuperscript{53, 54} Metastases may remain dormant for many years before becoming detectable. It is debated whether this dormancy represents a balance between cell growth and cell death or whether tumour cells are in cell cycle arrest.

Circulating tumour cells can be found in patients with uveal melanoma before any signs of clinically advanced disease.\textsuperscript{55, 56} Cells disseminated early might persevere as clinically dormant metastasis, later giving rise to distant recurrences.\textsuperscript{39} Uveal melanoma cells can remain dormant for longer than a decade, and metastasis-related deaths can occur more than forty years after diagnosis.\textsuperscript{57} This implies that metastatic cells may be quiescent in the liver for long periods before switching to an accelerated pattern of growth.\textsuperscript{58} A large meta-analysis of 5,433 patients from fifty-three studies looking at the detection of circulating tumour cells in patients with melanoma found insufficient evidence to conclude that circulating melanoma cells are a biomarker reliable enough to be clinically useful.\textsuperscript{59}
Malignant cells spread to distant sites by a process that requires invasion of the circulation. However, most tumour cells do not survive their journey in the bloodstream, and less than 0.1% remain to establish a new colony.\textsuperscript{11} Surviving cells attach to endothelial cells, causing retraction of the endothelium to expose the basement membrane. The tumour cells subsequently extravasate and grow in response to autocrine and local growth factors.

### 2.6 Vascular endothelial growth factor

Angiogenesis, or the formation of new blood vessels, is a complex process that occurs in normal physiology as well as disease. In 1983 Dvorak et al isolated a polypeptide they called vascular permeability factor.\textsuperscript{60} The same polypeptide was purified by Ferrara six years later and was named vascular endothelial growth factor (VEGF).\textsuperscript{61} VEGF is involved in angiogenesis and lymphangiogenesis during embryonic and postnatal development. It also plays a role in normal adult physiological processes including ovarian angiogenesis, tissue regeneration, haematopoietic stem cell survival, erythropoietin regulation and endochondral bone formation.\textsuperscript{62} Pathological processes such as neoplastic, haematological, ocular, inflammatory and ischaemic diseases also involve VEGF. In fact, so far-reaching are the processes involved that angiogenesis has been labelled an “organising principle” in biology and medicine.\textsuperscript{63}

The VEGF gene family consists of numerous members including VEGF-A, -B, -C, -D and placental growth factor. The most abundant and mitogenic member is VEGF-A, a multifunctional cytokine. VEGF-A increases microvascular permeability,\textsuperscript{60} induces endothelial cell migration and division, reprogrammes gene expression, promotes endothelial cell survival, prevents senescence, and induces angiogenesis.\textsuperscript{64} The expression, availability, and activity of VEGF-A is modulated by several mechanisms...
including hypoxia, oncogene and tumour suppressor dysregulation, transcription factors, inflammatory mediators, and mechanical forces.\textsuperscript{62}

VEGF-A is widely expressed by tumour cells and its action is primarily targeted towards vascular endothelial cells. In tumour angiogenesis, tumour cells and the surrounding tumour stroma release VEGF. Both uveal melanoma cells and the overlying retina produce VEGF-A, as well as other factors that promote invasion and metastasis.\textsuperscript{65, 66} This may indicate an autocrine-type induction of VEGF-A by the tumour on surrounding tissue.\textsuperscript{67} Tumour vascular endothelial cells express several-fold higher levels of VEGF receptors\textsuperscript{62} compared to normal vascular endothelial cells.

The regulation of VEGF-A in uveal melanoma is mainly controlled by hypoxia and involves the HIF-1\textalpha{} pathway.\textsuperscript{68} Phenotypically more aggressive tumours of larger height and basal diameter show higher levels of VEGF. Cell lines from uveal melanoma secrete several angiogenic factors including VEGF-A, which has been found in the aqueous and vitreous humour of affected eyes.\textsuperscript{69, 70} A study of VEGF-A concentrations in the aqueous humour of seventy-four untreated uveal melanomas found an almost three-fold increase compared to controls.\textsuperscript{67} Serum VEGF-A levels are increased in the presence of metastases.\textsuperscript{68}

Tumour growth does not occur continuously but rather in periods of rapid growth after dormancy. The concept of an “angiogenic switch” was postulated whereby the process of neovascularization of tumour cells allows rapid growth beyond the 1-2 mm limits of a non-vascularised metastasis.\textsuperscript{8, 71, 72} The angiogenic switch signals the rate-limiting transformation from hyperplasia to neoplasia and is regulated via environmental and genetic factors.\textsuperscript{8, 12} Sustained angiogenesis in uveal melanoma has been demonstrated by increased production of VEGF inducers in tumour cells and
accompanying inflammatory cells via upregulated expression of VEGF, IGF-1, IGF-1R, and raised levels of HIF-1α.\textsuperscript{13}

Tumour vessels stimulated by VEGF are structurally and functionally irregular, with necrotic cells, disordered blood flow, and increased permeability. Stasis and turbulent flow lead to further tumour hypoxia and consequent VEGF expression.\textsuperscript{70} The eye has no lymphatic drainage and uveal melanoma is a vascular tumour with almost exclusively haematogenous metastasis, making it a potential target for anti-angiogenic therapy.

A number of angiogenesis inhibitors have been approved for the treatment of cancer. The earliest drugs approved were bevacizumab (Avastin, Genentech/Novartis), a ligand-trapping monoclonal antibody, and two kinase inhibitors - sorafenib (Nexavar, Bayer) and sunitinib (Sutent, Pfizer) - targeting the VEGF receptor (VEGFR) tyrosine kinases, principally VEGFR2, type 2. Bevacizumab is a recombinant humanized monoclonal antibody targeting VEGF-A and all its isoforms. The United States Food and Drug Administration (FDA) approved it in 2004 for the treatment of advanced metastatic colorectal carcinoma based on a large, randomised phase III trial involving 813 patients which showed a five-month survival benefit when bevacizumab was added to standard chemotherapy versus chemotherapy alone.\textsuperscript{73} It is also used in combination with chemotherapy in the treatment of non-small cell lung cancer and breast cancer. Sorafenib and sunitinib have both been approved for the treatment of renal cell carcinoma, a highly vascular tumour.

Despite initial survival benefits, these VEGF inhibitors are failing to produce longstanding inhibition of tumour growth. Transitory improvements with a period of clinical benefit are followed by progression of the disease, suggesting an emergent
resistance to anti-angiogenic therapy. Two modes of resistance have been proposed: “evasive resistance”, with up-regulation of alternative pro-angiogenic pathways, and intrinsic or pre-existing non-responsiveness due to genetic ablation of the hypoxic response or the VEGF/VEGFR pathways. Monotherapy with a single angiogenesis inhibitor may not be sufficient and combining anti-angiogenic therapy with anti-invasive and anti-metastatic drugs may be a way to circumvent this problem.

Anti-VEGF treatments have revolutionised the management of many ocular conditions. VEGF has been implicated in the pathophysiology of multiple neovascular processes in human ocular conditions. Intravitreal bevacizumab has been studied in diseases such as age-related macular degeneration (ARMD), retinopathy of prematurity, diabetic retinopathy, radiation retinopathy and retinal vein occlusion. Ranibizumab (Lucentis, Novartis / Genentech) is a Fab antibody fragment that binds to all isoforms of VEGF. It is US FDA-approved for use in the eye and its efficacy in the treatment of ARMD has been demonstrated in large prospective, randomized controlled trials.

There have been case reports of bevacizumab as a treatment for intraocular tumours. A fifty-seven year-old woman with stage IV oestrogen receptor negative breast carcinoma treated with chemotherapy developed a choroidal metastasis that was treated with a high dose of bevacizumab (4 mg), resulting in a dramatic decrease in tumour size. Another case series reported three patients with choroidal melanoma initially misdiagnosed as choroidal neovascular membranes and treated with courses of bevacizumab at the standard dose of 1.25 mg/0.05 mL. The patients were treated with courses of either four or five bevacizumab injections, with two showing resolution of subretinal fluid. Two patients eventually underwent enucleation and histology demonstrated the formation of a subretinal fibrotic membrane overlying
the tumour. This feature had not been reported in a review of the histopathologic features of 1,527 globes with uveal melanoma. Dose-dependent reduction in size of intraocular melanoma in a murine model has been demonstrated after intraperitoneal injections of bevacizumab.

While there have been case reports of the use of bevacizumab in the treatment of uveal melanoma, to date no controlled studies have been published. There are many trials currently studying new angiogenesis inhibitors for advanced metastatic disease. A multicentre phase-II study involving 40 patients with inoperable stage III or IV metastatic uveal and cutaneous melanoma evaluated the VEGF trap aflibercept (Eylea, Regeneron). Half the patients treated (n=20) demonstrated four months of progression-free survival, and overall survival at one year was 56.4% compared to a predicted survival of 36%. Early results are promising, and further study on angiogenesis inhibitors is warranted.
CHAPTER 3
Clinical features

3.1 Epidemiology

Uveal melanoma is the most common intraocular malignancy and has the potential to cause blindness and death through metastasis. It is the most common non-cutaneous melanoma. The mean age-adjusted incidence of uveal melanoma has remained stable for decades, with rates about six per million per year in the United States.\textsuperscript{83,84} Men are at slightly higher risk than women, and peak incidence occurs at the age of seventy years, although individuals of any age can be affected.

Uveal melanoma usually occurs sporadically in the absence of obvious genetic predisposing factors. Unlike cutaneous melanoma, it is very rare for uveal melanoma to occur in families, although a handful of case reports have described familial uveal melanoma, usually affecting only two relatives. Affected families tend not to show features of a genetic predisposition, such as involvement over many generations, earlier age at diagnosis, bilateral involvement, multiple primary tumours, and phenotypic associations.\textsuperscript{32} These cases could in fact be explained by chance alone, given that the likelihood of uveal melanoma occurring in two individuals of a family of five is one in ten million.\textsuperscript{85} In 1905, Parsons described a family with a four-generation history of uveal melanoma and breast cancer. Immunohistochemical investigations of museum specimens of enucleated eyes from this family in the late 20\textsuperscript{th} century showed mutant p53.\textsuperscript{86} It is likely that this family is an early example of
the Li-Fraumeni syndrome, an autosomal dominant cancer predisposition syndrome owing to a germline p53 mutation.\textsuperscript{32}

### 3.2 Phenotypic associations

Phenotypes associated with uveal melanoma include fair skin, light iris colour, numerous cutaneous naevi, congenital ocular melanocytosis, oculodermal melanocytosis, uveal melanocytoma, familial atypical mole and melanoma syndrome, dysplastic cutaneous naevi, familial cutaneous melanoma and neurofibromatosis type one.\textsuperscript{6, 87}

Oculodermal melanocytosis describes congenital hyperpigmentation of the skin, episclera, orbit and meninges. Affected individuals also have excessive melanocytes in their uveal tract. This condition occurs thirty-five times more frequently in Caucasians with uveal melanoma compared to the general population.\textsuperscript{88} Followed for life, it is estimated that one in four hundred Caucasians with oculodermal melanocytosis will develop uveal melanoma.\textsuperscript{89} Consequently it is recommended that affected individuals are examined annually for signs of uveal melanoma. Patients with ocular and oculodermal melanocytosis who develop uveal melanoma have double the risk of metastasis compared to those without melanocytosis.\textsuperscript{90}

Neurofibromatosis type one (NF-1) is an autosomal dominant, multi-system disorder of neural crest-derived cells and has an incidence of one in 3,000. Affected individuals have excess cutaneous melanocytes, which manifest in the skin as café-au-lait spots, in the iris as Lisch nodules and in the choroid as naevi. Neurofibromatosis is also associated with neural crest-derived cell malignancies such as malignant schwannoma, phaeochromocytoma, and medullary carcinoma of the
thyroid gland. The NF-1 tumour suppressor gene is located on chromosome 17q11 and is known to regulate growth in neural crest cells such as melanocytes. About twenty cases have been reported in the literature of affected patients with uveal melanoma. This could however be coincidental; in one study, only one tumour in thirty-eight uveal melanomas studied contained a deletion in the NF-1 locus, with a resultant lack of neurofibromin expression.

3.3 Clinical presentation

Patients may have their melanoma diagnosed during a routine eye examination, but the majority have visual symptoms which include blurred vision, photopsia, and visual field changes. The classic appearance of a choroidal melanoma is a dome-shaped grey mass with surrounding exudative retinal detachment (Fig 3.1, 3.2). A “collar-stud” appearance occurs if the tumour breaks through Bruch’s membrane. The tumour is usually pigmented and has overlying orange lipofuscin, which sits at the level of the retinal pigment epithelium. Anterior or large melanomas may have prominent episcleral feeder vessels. Choroidal folds, haemorrhage, rubeosis, secondary glaucoma, cataract and uveitis may also occur if the tumour is large.
A number of lesions may mimic the appearance of a choroidal melanoma and it is important to consider other likely diagnoses. The large randomised Collaborative Ocular Melanoma Study (COMS) has shown that the misdiagnosis rate of large choroidal melanomas based on clinical examination, photographs, fluorescein
fundus angiography and ultrasound scan is 0.48%. However, selection criteria for the study itself was narrow, and difficult cases such as those with media opacities, ciliary body melanomas and pre-existing malignancies were excluded.

The differential diagnosis of a uveal melanoma is extensive. Haemorrhagic processes are common and can cause confusion. Subretinal haemorrhage from neovascular age related macular degeneration or a ruptured macroaneurysm may appear as a pigmented subretinal mass. Patients will usually have signs of macular degeneration in the other eye or a history of hypertension. A prominent vortex vein ampulla appears as a small, smooth brown dome-shaped lesion that disappears with external pressure on the eye. Congenital hypertrophy of the retinal pigment epithelium appears flat and pigmented with lacunae and well-defined margins. A melanocytoma is deeply pigmented with a feathery border and usually lies at the optic disc.

Up to 30% of uveal melanoma are amelanotic and there are a number of other lesions to consider when making this diagnosis. A choroidal metastasis is usually non-pigmented and appears at the posterior pole. There may be multiple or bilateral masses and the patient may not have a history of cancer. These tumours never have a collar-stud appearance. A choroidal haemangioma appears as an orange or pink dome-shaped mass at the posterior pole. Other non-pigmented lesions include choroidal granulomas which are small pale lesions associated with sarcoid and other uveitic conditions. Benign ciliary body lesions can mimic ciliary body melanoma. Iris and ciliary body cysts are not uncommon. Other rare ciliary body tumours include medulloepithelioma, adenocarcinoma, adenoma neurolemmoma, and leiomyoma. 6
3.4 Naevi and small tumours

It is estimated that fewer than one in 8,000 naevi undergo malignant transformation to uveal melanoma. A number of factors that predict growth in small choroidal melanocytic tumours have been identified. These include tumour thickness greater than 2 mm, posterior tumour margin touching the optic disc, visual symptoms (photopsia), orange pigment (lipofuscin), and the presence of subretinal fluid (Figures 3.3-3.5). Acoustic hollowness and absence of a halo are classic ultrasonographic features. Tumours with more risk factors are more likely to grow, with a median hazard ratio for those with one or two risk factors of three, rising to twenty-one for the presence of all seven factors.

Figure 3.3: Peripheral naevus with overlying drusen. The patient is asymptomatic, there is no subretinal fluid or lipofuscin and thickness on ultrasound is 3.5 mm, giving one risk factor for growth. Image courtesy of Professor ACB Molteno
Figure 3. 4: (above) Choroidal melanoma with subretinal fluid and margin involving the optic disc (courtesy of Professor ACB Molteno)

Figure 3. 5: Peripheral small choroidal melanoma with drusen, lipofuscin and subretinal fluid (courtesy Professor ACB Molteno)
Ancillary testing

Ultrasonography is the most useful ancillary test to aid diagnosis. Choroidal melanoma often show medium to low internal reflectivity with smooth attenuation on A-scan. Vascular pulsations may also be seen within the tumour. B-scan ultrasonography can provide useful information on the size and characteristics of choroidal or ciliary body melanoma. Melanomas are typically solid masses with low to medium internal reflectivity and a biconvex cross-sectional shape. Tumours display acoustic hollowing, with an acoustic quiet zone at the tumour base. Classically there is underlying choroidal excavation with shadowing of subjacent orbital soft tissue.

Choroidal melanomas characteristically display autofluorescence due to the presence of lipofuscin. Spectral domain optical coherence tomography (SD-OCT) allows impressive resolution of retinal and choroidal architecture (Fig 3.6). It is a potentially useful modality for tumours that are too small to be identified by conventional ultrasonography and is ideal for small (<3 mm) posterior pole tumours. Thickness measurements are on average 55% percent thinner using SD-OCT compared to ultrasonography. SD-OCT features of small choroidal melanomas are not always present, but include “shaggy photoreceptors” which indicate chronicity of retinal detachment, loss of external limiting membrane, and in some tumours loss of the inner segment-outer segment junction, irregularity of the inner plexiform layer, intraretinal oedema and irregularity of the ganglion cell layer (Fig 3.7). Image quality is limited by patient cooperation and media opacities. SD-OCT is also operator-dependent and cannot image thick tumours.
Figure 3.6: Nomenclature for normal anatomic landmarks seen on spectral-domain optical coherence tomography proposed and adopted by the International Nomenclature for Optical Coherence Tomography Panel.\textsuperscript{99}

Figure 3.7: Colour photos and SD-OCT of choroidal melanoma showing (B and E) slight elevation, optical shadowing and subretinal fluid and (C and F) "shaggy" photoreceptors.\textsuperscript{101}
Fluorescein fundus angiography (FFA) is not routine but may provide additional information and can identify masquerades such as choroidal neovascular membranes. There are no pathognomonic features of choroidal melanoma on FFA, but large melanomas characteristically have intrinsic vascularization, also known as a “double circulation”, referring to the simultaneous fluorescence of the retinal and choroidal vasculature within the tumour. Extensive leakage is often present, characterized by multiple pinpoint leaks (“hotspots”) at the level of the retinal pigment epithelium.

Computerized tomography (CT) scanning is more expensive than ultrasonography and has a limited role in the diagnosis of uveal melanoma. Choroidal melanomas show enhancement with contrast, which may differentiate it from a solid tumour or exudative retinal detachment. CT scanning will also detect calcification, a feature of choroidal osteomas.

Magnetic resonance imaging (MRI) scanning provides greater diagnostic value than CT but is less sensitive than ultrasonography. It is useful for detecting ciliary body melanomas and posterior extrascleral tumour extension. Most choroidal and ciliary body melanomas appear hyperintense relative to the vitreous on T1-weighted images and hypointense relative to the bright vitreous humour on T2-weighted images.

Positron emission tomography (PET) scanning is a relatively new modality that is increasingly being used to image uveal melanoma. PET scanning utilizes a radioactive form of glucose (18-fluoro-2-deoxyglucose, FDG) that taken up by highly metabolically active cells such as malignant tumour cells. It has low sensitivity and is expensive but can be useful to detect metastases. PET/CT scanning combines the
metabolic findings of PET with the anatomic characterization of CT. Some centres use PET scanning for baseline systemic evaluation. In a study of fifty patients, neither T1 tumours or small COMS choroidal melanomas were identified by PET/CT. Not all tumours larger than the 4 mm resolution limit were detected, confirming that high metabolic activity is integral to tumour detection using this modality.

3.6 Systemic evaluation

The choroid has the highest blood flow in the body and uveal melanoma is remarkable for haematogenous spread to the liver. Metastatic disease diagnosed using serum liver enzymes and liver ultrasound scanning is uncommon at diagnosis of the primary tumour, accounting for only 1-2% of patients. There is variation between centres in the level of screening undertaken to detect systemic disease. Some ophthalmologists perform a chest x-ray, liver ultrasound and serum liver enzyme panel in addition to a referral to an oncologist. Other centres screen for metastases in certain situations such as large tumour thickness to avoid unnecessary investigations and false-positive results.

3.7 Treatment options

It has long been known that for comparably-sized uveal melanomas, survival is independent of the method of treatment of the primary tumour. Despite the fact that most aggressive tumours have metastasized prior to diagnosis, failure to achieve local control is associated with increased risk of tumour-associated death. There are many treatment options shown to achieve local control, and patient- and hospital-based factors determine the most appropriate treatment for a given patient. Factors considered when deciding the most appropriate treatment include access to
treatment modalities, tumour location, size, visual acuity, intraocular pressure, growth rate, patient age, general health and the status of the fellow eye. Radiotherapy is the most common organ-sparing treatment for choroidal and ciliary body melanoma. Treatment options will be further discussed in detail in the following chapters.

3.8 Prognosis

Uveal melanoma is an aggressive cancer. Overall, there is a 50% chance of survival, but prognostication can be further stratified for an individual to do much better or worse. Survival prognosis correlates with clinical stage (TNM), histological grade and genetic type of melanoma. The single strongest indicator of prognosis in metastatic disease is the largest diameter of the largest metastasis, which has been incorporated into the current TNM anatomic classification (see Table 2.2).

As outlined in the previous chapter, multiple anatomic, histologic and molecular features have been identified that are poor prognostic indicators. Larger tumour size, ciliary body location, extrascleral extension, epithelioid cell type, and numerous mitotic figures all increase the risk of metastatic disease.\textsuperscript{41, 109, 110} Indicators of aggressive behaviour are chromosomal abnormalities involving monosomy 3 and gain of 8q.\textsuperscript{15, 20, 28, 34, 111} Almost all metastatic deaths occur in patients whose melanoma shows partial or complete loss of chromosome 3 on cytogenetic testing.\textsuperscript{20}

Epigenetic mechanisms such as histone modifications, DNA methylation, hydroxymethylation and non-coding RNA are critical to the regulation of the cell cycle, gene expression, apoptosis, phenotypic plasticity and other biologic functions in both normal and cancer cells. In 2004, Onken et al demonstrated that primary
uveal melanomas cluster into two distinct molecular classes based on gene expression profiling. They were able to separate uveal melanomas into low-grade (class one) and high-grade (class two) groups and showed that down-regulation of three genes (PHLDA1, FZD6 and ENPP2) accurately predicted metastatic death.\textsuperscript{111} The prognostic accuracy of these tests were subsequently confirmed by independent groups.\textsuperscript{112, 113}

The COMS trial of large melanoma studied 1,003 patients and found that of 435 patients who had died, 62\% had histologically confirmed metastatic melanoma at death and another 21\% had suspected metastases on the basis of imaging and tests but had no histological confirmation.\textsuperscript{114} The overall five- and ten-year metastasis rates of all patients enrolled in the large and medium COMS trials (2,320 patients) were 25\% and 34\% respectively.\textsuperscript{115} Long-term follow up of 289 patients in Finland with posterior uveal melanoma showed melanoma-related mortality rates of 31\% by five years, 45\% by fifteen years, 49\% by twenty-five years, and 52\% by thirty-five years.\textsuperscript{116}

Once metastatic disease has been diagnosed, in the largest unselected series of patients, the median survival time is 3.6 months, with a death rate of 80\% at twelve months, and 92\% at two years.\textsuperscript{115} Poor prognostic factors for survival time after detection of metastasis include older age, male gender, tumour symptoms, tumour diagnosis following symptoms, low Karnofsky index,\textsuperscript{117} short metastasis-free interval, hepatic involvement, numerous anatomic sites for metastasis, larger proportion of liver involved, and elevated liver enzymes.\textsuperscript{118, 119}
3.9 Surveillance of metastatic disease

Tumour dormancy refers to the disease-free period between clinical cure of the primary cancer and its subsequent local recurrence or distant metastasis. Based on melanoma doubling time, it has been calculated that most uveal melanoma metastases are initiated within five years before primary treatment.\textsuperscript{53} Metastatic cells can remain dormant for longer than a decade, and 40-50\% of patients with uveal melanoma have a greater than ten year disease-free interval.\textsuperscript{39}

The liver is the predominant organ involved in metastatic disease in 90\% of cases and median survival after diagnosis is approximately eight months.\textsuperscript{117} With concurrent liver imaging and serum alkaline phosphatase, chest x-ray screening does not yield additional benefit in diagnosing metastatic disease.\textsuperscript{117} A study of patients with metastatic uveal melanoma found that the chest radiograph and liver ultrasound were 100\% specific but had sensitivities of only 2\% and 14\% respectively.\textsuperscript{120} Numbers were small however: only 40 patients had a liver ultrasound and 223 had a chest x-ray.

Serum liver enzyme screening has low sensitivity and positive predictive value.\textsuperscript{122} Sensitivity indicates the probability of having raised liver enzymes in the presence of metastatic disease. Positive predictive value is the probability of metastatic disease in patients with raised liver enzymes. Isolated or combined liver function tests for aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transpeptidase (GGT) and lactate dehydrogenase (LDH) are not helpful in the detection of early metastases.\textsuperscript{122} Analysis of COMS patients with medium and large tumours who underwent screening for metastatic disease found that testing an individual liver function test (alkaline phosphatase, ALT, AST, GGT, LDH, or
bilirubin) provided high specificity (98%) but low sensitivity (0-19%) in detecting metastatic disease.\textsuperscript{123} False positive results may induce an unnecessary request for liver imaging. These markers do however have a relatively high negative predictive value, which may be of reassurance in the case of a negative test result. With normal liver enzymes, there is a 2.5% chance of metastatic disease being present.\textsuperscript{122}

A number of serum biomarkers have been identified that are increased before clinical diagnosis of metastatic disease. These include S100 beta, osteopontin, melanoma inhibitory antigen, and vascular endothelial growth factor.\textsuperscript{124} Insulin-like growth factor-1 has been shown to decrease with the development of uveal melanoma metastases six months prior to clinical detection and is a promising biomarker for metastatic disease.\textsuperscript{125}

Screening is “a health service in which members of a defined population... are asked a question or offered a test to identify those individuals who are more likely to be helped than harmed by further tests or treatments to reduce the risk of disease or its complications”.\textsuperscript{126} In 1968, the World Health Organisation proposed principles of screening which have been adapted for New Zealand by the National Health Committee.\textsuperscript{126} They recommend that eight criteria be used to assess screening programmes (Table 3.1).

Screening for metastatic disease in patients with uveal melanoma is controversial for a number of reasons. There is no good screening test for metastatic disease.\textsuperscript{120} Early detection of metastasis does not increase survival, but does lengthen the interval between metastasis and death due to detection bias. Micrometastases may occur years before treatment of the primary tumour.\textsuperscript{53} Metastases are usually highly and consistently chemoresistant.\textsuperscript{33}
Table 3.1: Criteria for assessing a screening programme

<table>
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<tr>
<td>▪ The condition is a suitable candidate for screening</td>
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<td>▪ There is a suitable test</td>
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<tr>
<td>▪ There is an effective and accessible treatment or intervention for the condition identified through early detection</td>
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<tr>
<td>▪ There is high quality evidence, ideally from randomized controlled trials, that a screening programme is effective in reducing mortality or morbidity</td>
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<tr>
<td>▪ The potential benefit from the screening programme should outweigh the potential physical and psychological harm (caused by the test, diagnostic procedures and treatment)</td>
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<tr>
<td>▪ The health care system will be capable of supporting all necessary elements of the screening pathway, including diagnosis, follow-up and programme evaluation</td>
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<tr>
<td>▪ There is consideration of social and ethical issues</td>
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<td>▪ There is consideration of cost-benefit issues</td>
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The potential benefits of screening for metastatic disease include reassurance for those with true negative test results, and knowledge of their situation for people with true positive results. Patients want to be informed of their prognosis, even if it is poor. Although earlier treatment can be offered to patients with positive results, there is no cure for metastatic uveal melanoma. Disadvantages of screening include longer periods of morbidity for patients whose prognosis is unaltered, resource costs, anxiety and risks associated with further investigations and treatment.

Periodic screening for metastases is thought to be beneficial when effective treatment is available or when patients are eligible to be candidates for clinical trials of promising treatment. A study of 298 patients with uveal melanoma
investigating their reasons for accepting cytogenetic testing and their reactions to results received found that the main benefit perceived by patients was that they would have greater control and that screening for metastatic disease and early treatment might enhance chances of survival. This was despite counselling that prognostication, screening and treatment are unlikely to prolong life. They found that almost all patients with uveal melanoma desire cytogenetic prognostication, and the only patient who regretted her decision had declined testing.

3.10 Treatment of metastatic disease

There are no prospective, randomised phase III clinical trials on treatment for metastatic uveal melanoma. Augsburger et al performed a literature search of articles on the effectiveness of treatment for metastatic uveal melanoma over a twenty-eight year period to June 2008. Of eighty identified publications, there were twenty-five phase I or II prospective clinical trials.

Treatment of metastatic disease requires aggressive intervention: metastectomy (surgical resection of metastatic tumours), systemic chemotherapy or regional therapies such as intrahepatic arterial chemotherapy and either embolization or chemoembolization of hepatic metastases. Median survival times in reported retrospective and prospective case series of metastatic uveal melanoma treated with these interventions range from 5.2 to 29.4 months.

Chemotherapy at present cannot stop the evolution of metastases. Chemoresistance is a major problem in oncology, illustrated by the fact that only one cancer in two is in long-term remission with chemotherapy. The multi-drug resistance phenotype expressed in uveal melanomas is complex and can vary considerably in its
components from one melanoma to another. A study of ninety-one consecutive patients who died of metastatic uveal melanoma found a median survival of 8.4 months from diagnosis for unselected patients and twelve months for those who received systemic chemotherapy.\textsuperscript{117}

The treatment of metastatic disease is controversial. Uveal melanoma is a rare disease and patient groups are highly selected before undergoing interventions to prolong survival with metastatic disease. Poor patient numbers mean insufficient power to make claims that any treatment can cause a clinically and statistically significant lengthening of overall survival compared to no treatment at all.\textsuperscript{129} Furthermore, there is likely to be a strong submission bias, where authors fail to submit negative or inconsequential reports, resulting in only positive studies in the literature.\textsuperscript{118} No randomized trials of treatment for metastatic uveal melanoma have been undertaken due to the rarity of the disease and lack of ability to achieve power.

By the time the primary tumour is detected, uveal melanoma is already a metastatic disease. Multiple studies have demonstrated late-onset metastatic disease up to forty years after successful enucleation of the primary tumour.\textsuperscript{116, 134} Quiescent tumour cells are resistant to conventional therapies that target rapidly dividing cells. Tumour dormancy is a poorly understood and unpredictable process. Maintaining tumour cells in their dormant state could however be considered an acceptable clinical endpoint if future therapeutic modalities allow prolongation of dormancy and prevent the development of clinically significant metastatic disease and death.\textsuperscript{135}

There has however been some success in prolonging survival with surgical resection of hepatic metastases.\textsuperscript{136-138} A large study at the Institut Curie followed 798 patients with metastatic uveal melanoma.\textsuperscript{136} Median survival was 4 months from diagnosis,
which increased to 8 months for patients who were treated with chemotherapy. A total of 255 patients underwent hepatic resection, which extended survival to 14 months. Survival was longer in patients who had a complete resection, fewer metastatic nodules, and were longer to develop metastases. Those with miliary lesions did worse. A smaller series of 35 patients found that those who underwent partial hepatectomy survived 3.7-fold longer than comparable patients who did not undergo surgery. Survival was longer in patients with one to five metastatic nodules and complete resection.\textsuperscript{137} In another study, twelve patients were treated with partial hepatectomy, of which eleven relapsed into metastatic disease with a median survival of twenty-four months.\textsuperscript{139} In 188 patients with a predicted 35\% five-year survival, ninety (48\%) developed metastases a median of eighteen months after diagnosis. Six-monthly hepatic MRI detected metastases before symptoms in 92\% of patients.\textsuperscript{139}
CHAPTER 4
Surgical management

4.1 Enucleation

Traditionally, uveal melanoma was treated by enucleation of the affected globe. In 1882, Ernst Fuchs (1851-1930) wrote that all intraocular melanomas were treated by enucleation, and untreated cases were only in the “older literature”. Enucleation remained the mainstay of treatment until the late 1970s, when doubt was cast on its efficacy. Zimmerman et al observed a peak in mortality in the second postoperative year following enucleation, and in a watershed article, postulated that manipulation of the globe during enucleation caused seeding of the tumour, accelerating metastatic death. They advocated a “no touch” technique for enucleation that avoided putting pressure on the globe. This theory later became known as the “Zimmerman-McLean-Foster Hypothesis” and stimulated widespread research into alternative treatments for uveal melanoma, including the Combined Ocular Melanoma Study (COMS).

Enucleation can be performed under local or general anaesthesia. It allows for the complete histologic examination of the eye and optic nerve and involves removal of the entire globe while preserving other orbital tissues. The surgeon must take care to avoid penetrating the globe during surgery and must handle the globe gently to minimize the risk of disseminating tumour cells. An orbital implant of sufficient volume is centred within the orbit and covered with Tenons and conjunctiva. Fornices should be deep enough to hold a prosthesis.
Enucleation is still performed for large uveal melanoma when there is no hope for useful vision with conservative treatment, when conservative forms of therapy fail, or on patient request. Features likely to result in primary or secondary enucleation include:\(^{145}\)

- Old age
- Tumour diameter exceeding 17 mm
- Tumour height greater than 10 mm
- Extensive involvement of optic disc, ciliary body, iris or angle
- Bulky extraocular extension
- Diffuse tumour growth
- Extensive retinal invasion or perforation

Compared to conservative forms of therapy, enucleation has not been shown to offer any survival advantage and does not accelerate metastatic death. The COMS group found that pre-enucleation radiotherapy does not improve survival.\(^{146}\) Primary enucleation is performed in about a third of patients with uveal melanoma and secondary enucleation is required in about 10\% of cases initially treated conservatively.\(^{147}\) Orbital tumour recurrence is rare if visible extraocular extension is not present at the time of enucleation.\(^{145}\)

Intraoperative complications of enucleation include removal of the wrong eye, anaesthetic complications from general anaesthesia (airway compromise, adverse drug reactions) or retrobulbar anaesthesia (globe perforation, brainstem anaesthesia, arterial injection of anaesthetic, orbital haemorrhage); bradycardia or asystole from stimulation of the oculo-cardiac reflex, orbital haemorrhage, incomplete enucleation if the eye is long or hypotonous, damage to the optic chiasm (and visual field of
contralateral eye) due to optic nerve stretch and extraocular muscle or nerve damage (resulting in poor motility of the prosthesis). Postoperative complications include infection, wound dehiscence, conjunctival cysts, implant migration or extrusion, socket contracture, ptosis, lash margin entropion, deep sulcus and complications associated with particular implants (e.g. hydroxyapatite implants).\textsuperscript{148, 149}

4.2 Tumour biopsy

With recent advances in molecular biology and genetics, obtaining tumour tissue for prognostication has become increasingly desirable as an adjunct to globe-conserving treatments. There are several different intraocular tumour biopsy techniques. These include aqueous tap, fine needle aspiration biopsy (FNAB) performed trans-sclerally or trans-vitreally, different vitrectomy approaches, endoretinal biopsy and external resection.

Indications for biopsy vary between centres with some units performing more biopsies than others. The main indication for FNAB is molecular prognostication, although it is also useful in the diagnosis of intraocular masses with atypical clinical findings.\textsuperscript{150, 151} It can also be useful in suspected metastasis with an unknown primary malignancy. Although 10\% of patients who present with uveal melanoma have a history of a primary malignancy elsewhere, about a third of patients presenting with intraocular metastases do not have a known history of cancer.\textsuperscript{152} Other indications for biopsy include discrepancy between non-invasive tests, patient insistence, re-growth following treatment and as part of study protocols.\textsuperscript{153}

Relative contraindications to FNAB include an intraocular tumour for which local resection is planned, as further preoperative testing is superfluous. In other
situations the risk of complications outweighs potential benefits, as in uveal melanoma for which a confident clinical diagnosis is made. Also, sampling small melanocytic lesions – which may be naevi or melanomas - may cause further diagnostic uncertainty and potential complications.\textsuperscript{154}

FNAB is being performed with increasingly smaller gauge needles and today can be performed with a 30-gauge needle. It is feasible to obtain RNA of adequate quality and quantity to perform transcriptomic analysis on uveal melanoma samples obtained via 25-gauge aspiration biopsy.\textsuperscript{155} Tumours >10 mm in diameter, >3 mm in height and located between the equator and optic disc can easily be sampled trans-sclerally. Exact placement of the needle is critical.

Complications of FNAB include endophthalmitis, retinal detachment, false negative results and tumour dissemination. False negative results are decreased by the presence of proficient local cytopathological services.\textsuperscript{153} Extremely small biopsy samples that are insufficient for accurate cytological diagnosis may still be able to undergo molecular profiling to give prognostic information.\textsuperscript{156}

\section*{4.3 Trans-scleral resection}

Trans-scleral or eyewall resection of uveal melanoma was first described in the 1960s by Stallard and Muller.\textsuperscript{157, 158} The technique has evolved considerably, yet remains technically challenging.\textsuperscript{159} It involves the removal of the intact tumour through a large opening in the overlying sclera, if possible without damaging adjacent retina.\textsuperscript{160}

Using a partial thickness lamellar scleral dissection, the tumour is resected from the eye with a surround of healthy choroid and the inner scleral lamella, which is in
contact with the tumour. The retina is left intact. The operation is performed under profound hypotensive anaesthesia. Adjunctive brachytherapy with a ruthenium plaque is administered, either if clearance is uncertain, or according to the surgeon’s preference.

Trans-scleral resection is a treatment alternative to enucleation in selected patients and allows globe retention. Contraindications to trans-scleral local resection include:

- Being unfit for hypotensive anaesthesia
- Involvement of the optic disc or more than a quarter of the ciliary body, iris or angle
- Diffuse tumour growth
- Extraocular extension
- Extensive retinal invasion or perforation

Most large tumours occur in older patients, of whom many have co-morbidities that preclude the use of hypotensive anaesthesia. Many patients require additional surgery for postoperative complications. These include post-operative vitreous haemorrhage, retinal detachment and cataract. Residual tumour is the main complication of trans-scleral resection. Risk factors for tumour recurrence include largest basal diameter \( \geq 16 \) mm, advanced age, retinal detachment, posterior tumour extension and epithelioid cell type. Adjuvant radiotherapy of the tumour area has been shown to reduce tumour recurrence.
4.4 Endoresection

Developed independently by Peyman\textsuperscript{164, 165} and Damato\textsuperscript{166}, primary endoresection is highly controversial. It is usually performed with adjunctive ruthenium brachytherapy.\textsuperscript{160} After a standard 3-port vitrectomy, the tumour is removed with a vitreous cutter from beneath the retina via a retinotomy.\textsuperscript{160} Haemostasis is achieved by raising intraocular pressure and moderate hypotensive anaesthesia. The retina is re-attached using fluid-air exchange and endolaser is used to create a firm adhesion around the retinoplexy and to treat any cells that might be left on the scleral surface. The air is replaced with silicone oil, which is removed twelve weeks later. Cryotherapy is applied to the sclerostomies, and adjunctive ruthenium plaque brachytherapy is used in selected cases.

Endoresection has been described as a primary procedure for tumours that are not expected to do well after more conventional forms of treatment, or as a salvage procedure for patients anticipated to respond poorly to other types of treatment.\textsuperscript{166} As a secondary procedure, endoresection can be used after radiotherapy to treat exudative maculopathy or to remove apparently active tumour.\textsuperscript{167} Suitable tumours include those extending to within one disc diameter of the optic disc, and growing tumours previously treated by radiotherapy.\textsuperscript{166} The main contraindications are involvement of more than a third of the optic disc margin and tumour diameter exceeding 10 mm.\textsuperscript{145} Endoresection does allow for histological and cytogenetic processing of the tumour.

Several case series have been reported, and complications include retinal detachment and cataract formation.\textsuperscript{165, 166, 168} A recent review of local treatment failure after globe-conserving treatment of uveal melanoma found that surgical resection has a higher
rate of local treatment failure compared to radiotherapy.\textsuperscript{169} Endoresection following proton beam therapy has been shown to reduce the risk of subsequent neovascular glaucoma.\textsuperscript{170} Some ocular oncologists believe this technique is highly controversial and have expressed concern about the possible intraocular dissemination of tumour cells at the time of surgery, the lack of prior evaluation in an animal model, and short period of follow up.\textsuperscript{171} It would be difficult to justify endoresection for tumours that can satisfactorily be treated by more conventional methods which are explained in the following chapter, such as plaque radiotherapy.\textsuperscript{166}
CHAPTER 5
Radiotherapy

5.1 Radiation

Professor Konrad Röntgen first discovered electromagnetic radiation in the Bavarian city of Würzburg in 1895. This “new kind of light” was described as “a discovery so strange that its importance cannot yet be measured, its utility be even prophesized, or its ultimate effects upon long established scientific beliefs be even vaguely foretold... Röntgen has given it the name of the X-rays”.¹⁷² He was awarded the first Nobel Prize in 1901 “in recognition of the extraordinary services he has rendered by the discovery of the remarkable rays subsequently named after him”.¹⁷³ Two years later Henri Becquerel and Pierre and Marie Curie were awarded the Nobel Prize for the discovery of spontaneous radioactivity.¹⁷⁴ Subsequent research uncovered the therapeutic properties of radiation.

5.2 Radiotherapy

Radiotherapy has a long history as a medical therapy. In 1896, less than sixty days after the discovery of X-rays, Emil Grubbé treated an advanced ulcerated breast cancer with X-rays in Chicago.¹⁷⁵ Radiotherapy capitalizes on the energy created by the interaction of sub-atomic particles with each other, which can break chemical bonds and create ions such as oxygen radicals. Ions are created when an atomic particle or photon hits another atom, resulting in loss of a proton, neutron or
electron. These ions interact with DNA, causing single- or double-strand breaks, base-pair alterations, and interfere with a cell’s ability to repair and duplicate.

Radiation can take the form of electromagnetic waves, particles, or both. Electromagnetic (photon) radiation consists of wavelengths from $10^{-7}$ m to $10^{-13}$ m. Linear accelerators produce photon beams with wavelengths in the range of $10^{-11}$ m to $10^{-13}$ m. Particle radiation can be electrically charged (protons, electrons) or uncharged (neutrons, photons) and interacts with matter by transferring energy as it travels through a medium.

Radioactive decay is the process by which the atomic nucleus of an unstable atom loses energy in order to return to a stable, low-energy state. Brachytherapy, gamma-knife radiotherapy, and cobalt-60 machines employ this method. Three types of radiation can be emitted by the nucleus during this process: positively charged $\alpha$-particles (helium nucleus), negatively charged $\beta$-particles (electrons), and $\gamma$ rays with no charge.

Teletherapy is the process of delivering ionizing radiotherapy at some distance from the patient. A cobalt-60 unit holds a radioactive cobalt source that emits $\gamma$ radiation as it decays to nickel-60. The energy of the $\gamma$ photon beam is 1.25 million volts (MV), with the maximum dose being delivered to a depth of 0.5 to 1.0 cm. A linear accelerator is a type of particle accelerator that uses high-frequency electromagnetic waves to accelerate charged subatomic particles or ions to high energies through a linear vacuum tube. Maximum energies range from 6 to 19 MV, with 80% of the maximum dose delivered to a depth of 2 to 6 cm.
Neutron and proton beams have a higher linear energy transfer than photons, meaning they release more energy and cause more damage as they pass through tissue compared to photons and electrons. A heavy particle accelerator called a cyclotron can produce these beams. Proton beams have a characteristic dose distribution termed the Bragg peak, with a steep peak of maximal dose and sharp subsequent drop-off, which means that most of their energy is deposited at the end of its range. The Bragg peak can be manipulated to conform to any tumour size by varying the beam energy and is useful for the treatment of tumours located near critical structures such as the optic disc or macula.

5.3 Biologic basis of radiation therapy

Ionizing radiation is characterized by an ability to ionize or expel electrons from atoms and molecules. Tissue damage caused by ionizing radiation is due to the ejected electrons themselves, which travel at high speeds and randomly go on to cause a cascade of further ionizations in the molecules and atoms they collide with. Each interaction costs energy and the electron eventually slows to the point where it is captured by an atom, molecule or ion, causing the formation of a free radical. Usually the electron is captured by water, the most abundant molecule in the cell, and reactive oxygen species are formed. These can cause structural alterations in DNA, affect cytoplasmic and nuclear signal transduction, modulate the activity of proteins and genes that respond to stress and regulate cell proliferation, differentiation and apoptosis.177

Ions may also directly interact with DNA, resulting in single-strand breaks, double-strand breaks, or base-pair alterations, thus impairing a cell's ability to regenerate and duplicate. Clusters of ionizations can occur within a few base pairs of DNA,
which is present in only two copies and has limited turnover, making it vulnerable to permanent damage. As a result, there are complex processes within cells to repair DNA. Two main groups of signalling pathways known as sensors and effectors are responsible for this process. Proteins actively survey the genome for damage and activate three main effector pathways, leading to programmed cell death (apoptosis), DNA repair, and temporary or permanent blocks in the cell cycle in response to damage.\textsuperscript{178}

Two important proteins in the effector pathway are p53 and MDM2. The function of p53 is to regulate genes that control both cell-cycle checkpoints and apoptosis. One of the most commonly mutated tumour suppressors, p53 is regulated at the protein level by binding to its partner MDM2 and being inactivated. DNA damage checkpoints are specific points in the cell cycle at which progression of the cell into the next phase can be blocked or slowed. There is a checkpoint at the transition between G1 and S phases, the point where the cell decides to initiate cell division (figure 5.1).

Double stranded DNA breaks are the most important and difficult lesion to repair. There are two ways to repair these lesions. Homologous recombination uses the undamaged sister chromatid sequence as a template for repair. This process takes hours and can only occur while the cell is dividing in late S- and G2-phases (see figure 5.1). Non-homologous end joining is a ‘quick and dirty’ way of repairing double stranded DNA breaks.\textsuperscript{178} Two DNA double stranded breaks are joined together without requiring homologous DNA sequences. This is less accurate than homologous recombination but occurs in all phases of the cell cycle, is more rapid and maximizes a cell’s chance of survival.
The radiosensitivity of cells varies significantly throughout the cell cycle. Cells are most resistant to ionizing radiation when they are resting in G0 phase. After a dose of radiation, cells either halt at G1/S or G2/M checkpoint and repair is attempted. After a number of hours, most cells that are not successfully repaired will be halted at G2, unless their cell cycle checkpoints have been damaged. A second dose of ionizing radiation will therefore hit more cells in their vulnerable G2 phase, causing further damage to DNA. With increasing time after irradiation, cells will become more evenly distributed across the cell cycle, a phenomenon referred to as redistribution.

Bergonié and Tribondeau described the concept of radiosensitivity in 1906 and offered a prediction about the relative sensitivities of different types of cells to radiation. They concluded that the radiosensitivity of a cell is directly proportional to its reproductive activity and inversely proportional to its degree of differentiation. Cells tend to be radiosensitive if they have a high cell division rate, a high metabolic rate and an unspecialized phenotype. A single dose of radiation sufficient to control a population of rapidly growing cancer cells may result in severe normal tissue injury. By dividing the total dose of radiation into smaller doses over a period of several days, the differential between normal tissue and tumour response to radiation is enhanced and toxic effects on healthy cells are minimized.
Regaud and Ferroux showed in 1927 that differential radiosensitivity of tissues – in this case skin and testis - was increased with dose fractionation.\textsuperscript{183} A single dose of radiation sterilized the testis but caused skin necrosis, whereas sterilization could still be achieved with minimal skin reaction if the same dose was given in small fractions over a period of weeks. This finding has important implications for radiotherapy – by fractionating the dose, growing cancers can be treated with relative sparing of normal tissue. A number of factors have been shown to influence the outcome of fractionated-dose radiotherapy.

The mechanisms by which fractionation improves targeted killing of tumour cells can be explained by the four R’s of radiotherapy: repair of sub-lethal injury in normal and neoplastic cells, re-oxygenation of the tumour, redistribution through the cell division cycle, and repopulation of surviving normal and malignant cells between dose fractions.\textsuperscript{184} Intrinsic cellular radiosensitivity has been suggested as a fifth ‘R’ to account for the different tolerance of tissues to fractionated irradiation.\textsuperscript{180}

Fractionation is beneficial for many normal tissues that proliferate relatively slowly and have time to repair damage before replication. Tumour tissue that is rapidly proliferating is less able to repair lethal damage to DNA before replication. Fractionation also increases damage to the tumour by allowing re-oxygenation of hypoxic cells, making them more sensitive to the subsequent dose of radiotherapy.\textsuperscript{185} Cells are most resistant to radiation damage when they are in the S phase of the cell cycle. After a large dose of radiation, most of the surviving cells will be in the S phase and a second dose will be effective only once cells have been given time to redistribute throughout the cell cycle before the second dose is given.
Melanomas are known to be radioresistant\(^\text{186}\) and melanoma cells have a greater ability than most tumour cells to repair potentially lethal cellular damage between fractions of radiotherapy.\(^\text{187}\) They also have a large proportion of poorly oxygenated cells which are generally less sensitive to irradiation than well-oxygenated cells.\(^\text{185}\) This means that high doses of radiation must be given to kill tumour cells.

### 5.4 Plaque brachytherapy for uveal melanoma

Radiotherapy is the most common organ-sparing treatment for choroidal and ciliary body melanoma. The two main types of radiation therapy used in the treatment of uveal melanoma are brachytherapy and external beam radiotherapy. Brachytherapy utilizes sealed radioactive sources that are placed in direct contact with the tissue to be treated. External beam radiotherapy is a type of radiotherapy where the radiation source is outside the body.

Brachytherapy was first used to treat uveal melanoma in the 1920s by means of radon seeds that were inserted directly onto the intraocular melanoma.\(^\text{188, 189}\) Radium applicators replaced radon seeds as they provided a more homogenous field of radiation. Stallard was the first ophthalmologist to successfully treat patients with cobalt-60 plaques, publishing a series of 100 patients treated from 1939 to 1964.\(^\text{190}\) Plaques used historically include radon gas encapsulated in gold seeds,\(^\text{191}\) beta-ray applicators, and cobalt plaques. Cobalt-60 plaques are infrequently used today, and other isotopes that have been used are strontium-90, iridium-192, and palladium-103 (see Table 5.1).\(^\text{140}\) Isotopes in common use today include iodine-125 and ruthenium-106.
The inverse-square law demonstrates that the fall-off in dose with brachytherapy is inversely proportional to the square of distance from the radiation source. Thus, a high radiation dose at the tumour apex requires a much higher dose at the tumour base. This is why there is a limit to the thickness of tumours able to be safely treated with plaque brachytherapy.

In 1949 Freundlich described ruthenium-106 (Ru\textsuperscript{106}) as a candidate for high-dose local irradiation\textsuperscript{192}. The radioisotope Ru\textsuperscript{106} decays via rhodium-106 to produce the stable element palladium-106, producing beta radiation. Tumours best suited for Ru\textsuperscript{106} therapy are usually less than 6 mm in height above the scleral surface, lie at least two disc diameters from the optic nerve head, and do not involve the ciliary body or extend outside the eye\textsuperscript{193}. However, some centres treat thicker tumours and also treat peripapillary melanoma with notched plaques.

Cobalt-60 is a high-energy plaque and can be used to treat thick tumours but also is associated with an increased incidence of radiation-induced side effects. Iodine-125 is

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### Table 5.1 – Isotopes used in plaque brachytherapy of the eye

<table>
<thead>
<tr>
<th>Isotope</th>
<th>Cobalt 60</th>
<th>Iridium 192</th>
<th>Ruthenium 106</th>
<th>Gold 198</th>
<th>Palladium 103</th>
<th>Iodine 125</th>
</tr>
</thead>
<tbody>
<tr>
<td>Energy (MeV)</td>
<td>1.25</td>
<td>0.38</td>
<td>3.5</td>
<td>0.42</td>
<td>0.21</td>
<td>0.032</td>
</tr>
<tr>
<td>Type</td>
<td>Gamma</td>
<td>Gamma</td>
<td>Beta</td>
<td>Gamma</td>
<td>Gamma</td>
<td>Gamma</td>
</tr>
<tr>
<td>Half-life</td>
<td>5.2 years</td>
<td>74 days</td>
<td>366 days</td>
<td>3 days</td>
<td>17 days</td>
<td>59 days</td>
</tr>
<tr>
<td>Half value layer (mm)</td>
<td>11</td>
<td>Lead</td>
<td>Lead</td>
<td>Lead</td>
<td>Lead</td>
<td>Lead</td>
</tr>
<tr>
<td>10\textsuperscript{6} energy transmission opposite side (mm)</td>
<td>25</td>
<td>Lead</td>
<td>Lead</td>
<td>Lead</td>
<td>Lead</td>
<td>Lead</td>
</tr>
<tr>
<td>Advantages</td>
<td>Long half-life</td>
<td>Ease to customize</td>
<td>Sharp fall off</td>
<td>Good energy</td>
<td>High dose rate</td>
<td>Ease to customize/shield</td>
</tr>
<tr>
<td>Disadvantages</td>
<td>Difficult to shield</td>
<td>Difficult to shield</td>
<td>Only thin tumors</td>
<td>Short half-life</td>
<td>Short half-life</td>
<td>Short half-life</td>
</tr>
</tbody>
</table>

half-life \textsuperscript{50\%} of total energy released by isotope in a given time; half-value layer = shielding necessary to reduce isotope energy to \textsuperscript{50\%}; \textsuperscript{10\%} energy transmission opposite side = shielding necessary to reduce isotope energy to \textsuperscript{10\%} energy transmission on the opposite side of the plaque.
used commonly and was studied in the COMS trial in the treatment of medium-sized tumours 2.5-10 mm in apical height.\textsuperscript{45} Plaques can be fashioned to fit the size of the tumour and are sutured to the sclera after careful localization with transillumination. The plaque is removed after the appropriate dose of 10,000 rad (100 Gray) had been delivered to the apex with seven to fourteen days exposure time.

Local tumour control is an important goal of plaque brachytherapy and tumour recurrence is significantly associated with decreased survival.\textsuperscript{194, 195} Most posterior melanomas do not disappear completely after radiation treatment, but show significant reduction in size. Risk factors for relapse include older age, greater tumour thickness and diameter,\textsuperscript{196} and proximity of the tumour to the foveal avascular zone\textsuperscript{195} and optic disc.\textsuperscript{194}

5.5 Collaborative Ocular Melanoma Study (COMS)

In the 1970s, Zimmerman suggested that enucleation of eyes with uveal melanoma accelerated metastatic death by disseminating tumour cells into the general circulation.\textsuperscript{141} At the same time, Manschot declared that radiotherapy of uveal melanoma was unjustifiable. He histologically showed viable tumour cells after radiotherapy and vociferously advocated early enucleation.\textsuperscript{197} Studies addressing survival between enucleation and radiotherapy showed no significant differences but were nonrandomized with inadequate patient numbers and short follow-up.\textsuperscript{198}

The Collaborative Ocular Melanoma Study (COMS) was started in 1985 as a multicenter randomized clinical trial comparing radiotherapy to enucleation, and hoped to resolve the dilemma concerning treatment selection for uveal melanoma. Funded by the National Eye Institute, it is the only source of level II evidence for the
management of primary ocular melanoma. COMS was a three-arm study that included two multicentre randomised clinical trials designed to compare (a) the effectiveness of brachytherapy to enucleation for the treatment of medium-sized choroidal melanomas, and (b) the effectiveness of enucleation with and without preoperative external-beam radiotherapy for large choroidal melanomas. The third arm was an observational study of small choroidal melanomas. Patient recruitment ran from 1987 to 1998.

In the COMS large choroidal melanoma trial, 1,003 patients were studied with choroidal melanomas over 16 mm in basal diameter and/or over 10 mm in apical height. Subjects were randomised into treatment with enucleation alone or enucleation preceded by external beam radiotherapy with a dose of 20 Gy (Gray). Five-year survival rates were 57% for enucleation alone, and 62% for enucleation plus radiotherapy. Adjunctive radiotherapy did not improve overall survival, confirming previous studies, and suggesting that clinically undetectable metastases at the time of diagnosis were responsible for many of the deaths of patients with large choroidal melanoma. COMS failed to find any survival difference between rival treatments due to insufficient statistical power.

Brachytherapy was selected for the radiotherapy arm of the COMS medium choroidal melanoma trial because of the small number of facilities equipped to deliver charged particles. They recruited 1,317 patients with choroidal melanomas ranging from 6 to 16 mm in basal diameter and/or 2.5 to 10 mm in apical height. Standardized enucleation was compared to iodine-125 brachytherapy, delivering 85 Gy to the tumour apex. All-cause mortality at five years was 18% in the enucleation group and 19% with brachytherapy. Histologically confirmed metastases at five
years occurred in 9% of patients treated with brachytherapy as opposed to 11% of patients who underwent enucleation. In the brachytherapy group, there was a 10.3% local tumour recurrence rate at five years. Enucleation after brachytherapy at five years occurred in 12.5% of individuals. Local tumour recurrence was weakly associated with a reduced survival (adjusted risk ratio of 1.5). Decline in visual acuity to 20/200 occurred in 43% at three years. Six lines of visual loss occurred in 49% at three years. Only two in 660 (0.3%) enucleated eyes were misdiagnosed as having a choroidal melanoma.

The COMS small choroidal melanoma trial was an observational study of 204 patients with tumours measuring 4 to 8 mm basal diameter and/or 1.0 to 2.4 mm in apical height. Melanoma-specific mortality was 1% at five years. Clinical growth factors included greater initial thickness and basal diameter, presence of orange pigmentation, absence of drusen and/or retinal pigment epithelial changes, presence of tumour pinpoint hyperfluorescence on angiography.

5.6 Proton therapy

Proton therapy is a type of external-beam radiotherapy that was first suggested as a cancer treatment in 1946\textsuperscript{204} and began in 1976 as a treatment for uveal melanoma.\textsuperscript{205,206} Protons are positive, charged particles, about 2,000 times the mass of an electron. They travel through matter in straight lines, unlike electrons of the same penetrating power, which are scattered. In contrast to electrons, protons of the same energy will stop at the same depth. The density of ionization along the proton pathway increases with distance, due to increased energy loss from interactions with electrons. This results in a pronounced increase in dose at the end of the pathway of a proton, known as the Bragg peak of ionization. Almost no dose is deposited in the normal
tissue beyond the Bragg peak. The energy of a beam of protons can be modulated using a combination of protons of different energies, or by scattering the beam to broaden the size and depth of the Bragg peak. This allows for localized delivery of ionizing radiation. The use of charged particles permits delivery of equivalent tumour doses much higher than can be delivered with standard photon therapy, and thus higher local control and survival rates are possible.\textsuperscript{207}

A more homogenous dose of radiation energy is delivered to the tumour with proton therapy than with a radioactive plaque, which delivers more energy to the base of the lesion. Proton therapy is an alternative treatment for tumours that cannot be satisfactorily treated with episcleral plaque brachytherapy due to tumour thickness or proximity to the optic nerve and other vital structures.\textsuperscript{208} Because of the ability to deliver a high dose to a sharply confined target volume, there is a high local control rate (about 96%), a high rate of retention of the eye (85 to 94%) and preservation of visual acuity of 20/200 or better in 35 to 75% of patients, depending on the size and location of the tumour.\textsuperscript{207} Complications may arise due to radiation of the anterior segment, and manifest most severely as neovascular glaucoma, which occurs in 10% of treated eyes. Vision loss occurs in approximately 50%. The main disadvantage of proton and ion therapy is the significant cost of the equipment, maintenance and staffing needed for such a facility.

5.7 Helium ion therapy

Helium ion therapy, like proton therapy is widely used for the treatment of medium-sized tumours. Helium ions contain higher linear energy transfer than protons, meaning that they transfer more energy to the matter they pass through. They therefore have a greater chance of causing injury to normal tissue anterior to the
tumour. In the treatment of a posterior choroidal melanoma, the sharply defined helium ion beam passes through the anterior portion of the eye. This results in higher irradiation of anterior structures and less radiation to uninvolved regions of the posterior pole compared with a brachytherapy source sutured to the sclera. Presumably because of this difference in radiation distribution, anterior segment complications are seen more frequently with particle beam treatment, while posterior complications are more common with radioactive plaques.\textsuperscript{209}

5.8 Stereotactic radiosurgery and radiotherapy

Stereotactic radiosurgery (SRS) and stereotactic radiotherapy (SRT) are techniques that rely on the anatomical confinement of the high-dose volume. They are techniques which tightly focus a damaging dose of radiation on a target while giving surrounding tissues a low and safe dose. SRS is a total dose given in a single treatment event (fraction) and can be given by either a Gamma-knife (using multiple cobalt-60 sources) or a linear accelerator. Gamma knife SRS accuracy is enhanced by surgical placement of tantalum markers prior to radiotherapy. SRT involves several or multiple fractions given by linear accelerator and markers are not used. Precisely directed external-beam radiation is delivered from a number of angles to converge on the tumour and limit the total dose of radiation to normal tissue. Fractionation allows normal tissue to recover between doses, thereby minimising the margin of normal tissue included in the radiation treatment volume, and reducing radiation-related complications.

Fractionated SRT (SRT) is delivered using an eye fixation and monitoring system. Patient immobilization is critical to allow precise tumour treatment and limit intra-fractional patient motion that would otherwise necessitate the use of larger safety
margins or repeated verification for each treatment field.\textsuperscript{210} In a study of immobilization devices, the modified Gill Thomas Cosman frame (GTC) provided the best control of intra-fractional patient motion and had a 1 mm limit of relocation. There was a 95\% probability of observing a three-dimensional vector length of motion of less than 1.8 mm.\textsuperscript{210} The GTC frame also allows for relatively fast and reproducible setup of the patient at the start of a treatment fraction.

A light source for fixation is attached in front of the healthy or diseased eye, which is continuously monitored on a small camera integrated into the mask system. Eye movements are viewed on a TV screen in the control room by the radiation oncologist who marks the position of the pupil and iris. Treatment is immediately stopped if the eye deviates from the primary position.

Treatment planning is based on CT images acquired with the patient in the fixation device and their eye in the primary position. Planning for small tumours that are not visible on CT scanning is based on clinical photographs. The visible tumour extension on CT is known as the gross target volume of the tumour. The clinical target volume extends a margin around this to cover microscopic tumour extension. Planning target volume is the volume ultimately treated: clinical target volume plus a safety margin of 2 mm in all directions, accounting for set-up variations and organ motion. The total dose of radiation for a tumour depends on tumour responsiveness, the extent of microscopic disease, treatment aims (cure or palliation) and the limitations of surrounding tissues. Uveal melanoma is considered to be relatively radioresistant, and critical structures surrounding the tumour (lens, optic nerve, lacrimal gland, opposite orbit) are vulnerable to damage from radiation. Typical doses for uveal melanoma delivered with a 2100 c linear accelerator are 40 to 60 Gy
with the 80% isodose encompassing the planning target volume and consist of five to seven arcs of radiation. All treatments are given in fractions over five to ten days.

5.9 Side effects of radiotherapy

Ionizing radiation damages cellular DNA and other vital cellular structures leading to either immediate cell death or mutations that can take years to cause cell death. A number of factors increase the radioresistance of tumour cells, including hypoxia, acidosis and free-radical scavengers. A long-term effect of radiation injury is vascular damage, primarily due to pericyte death, which usually takes years to develop. With plaque radiotherapy, ionizing radiation travels from the plaque through the underlying sclera to the choroidal tumour, then on through the retina and vitreous to the other side of the eye to exit the globe. Radioactive plaques deliver their radiation dose to the structures immediately beneath and around them which may explain why there is a higher rate of radiation retinopathy than with other forms of treatment.\textsuperscript{211}

External beam charged-particle radiotherapy (helium and proton therapy) is delivered via a cyclotron and radiation is directed to the tumour usually from an anterior approach. Ionizing radiation passes through eyelids, cornea, sclera, iris, lens, vitreous and retina to reach the tumour. Subsequently, these structures may develop radiation-related damage, and reports describe a predominance of anterior segment complications.\textsuperscript{212}

The vascular effects of radiotherapy are due to intimal thickening and consequent reduction in vessel diameter.\textsuperscript{6} Poiseuille’s equation states that flow is directly proportional to the 4th power of the radius; thus reduction in vessel diameter causes
vascular insufficiency. Radiation retinopathy results in ischaemia – capillary dropout – and exudation – retinal haemorrhages, lipids and oedema. Histopathological studies show an obliterative endarteritis characterised by endothelial cell loss and thickened vessel walls, leading to microaneurysms, arteriovenous shunt vessels and subsequent neovascularization.\(^6\) The risk of radiation retinopathy is related to effective dose, the presence of systemic disease (such as diabetes mellitus) and the use of radiation sensitisers such as chemotherapy. Laser photocoagulation can be used to control radiation retinopathy but radiation maculopathy usually results in blindness.

Radiation maculopathy develops in approximately 50% of eyes, with poor visual outcome. Late complications include macular destruction because of scarring around the tumor, optic nerve atrophy, macular degeneration, post-radiation retinopathy, cataract, vitreous hemorrhage, secondary glaucoma, thrombosis of the central retinal vein, scleral necrosis.\(^{213}\) There have been many articles published on the role of bevacizumab in the treatment of radiation maculopathy.

A recent review found that treatment of radiation maculopathy with anti-VEGF agents or steroids are effective at reducing macular thickness and improving visual acuity.\(^{214}\) They found that there was significant variation in the effect of bevacizumab between patients, and a variable requirement of anti-VEGF therapy between studies, which may not be completely explained by variations in treatment regimes and follow-up. Other treatments that have been used include photodynamic therapy, laser and hyperbaric oxygen.\(^{214}\)

Exposure to all types of therapeutic ionizing radiations can result in cataract formation. The lens is the most radiosensitive ocular structure. It shows clinically
visible damage with 0.5 Gy within two to three years\textsuperscript{215} and there is no threshold for cataract development.\textsuperscript{216} Classically, radiation cataract is described as a posterior subcapsular opacification, sometimes with a "doughnut" configuration in the early stages.\textsuperscript{212} Damage to lens epithelial cell DNA is responsible for most radiation cataracts. Genomic damage deranges lens fiber differentiation and abnormal lens epithelial cells migrate to form a posterior subcapsular opacity. Radiation appears to increase the burden of aberrant cells and to hasten cataract onset.

The sclera is the ocular structure most tolerant of ionizing radiation. Scleral necrosis usually develops within five years and has an incidence of 1\% (73 of 5,057) of patients treated with plaque brachytherapy, although it may remain undetected in eyes with posterior tumours.\textsuperscript{215} Plaque radiotherapy requires a dose of 80 to 100 Gy of iodine-125 to the tumour apex, resulting in a dose of 350 to 400 Gy to the sclera and tumour base. Risks for scleral necrosis include ciliary body and anterior tumour location, tumour thickness $\geq$6 mm, and radiation dose $\geq$400 Gy to the outer sclera.\textsuperscript{215}

Other complications of radiotherapy include neovascular glaucoma, optic neuropathy, chemosis, choroidal detachment, and exudative retinal detachment.\textsuperscript{213} Factors related to poor visual outcome, including greater tumor thickness, closer proximity to optic disc and foveola, submacular fluid, worse pretreatment vision, and increasing radiation dose to optic disc, foveola, and lens.\textsuperscript{217}

\section*{5.10 Transpupillary thermal therapy}

Infrared laser thermal therapy, referred to as transpupillary thermal therapy (TTT), was initially described as an adjunct to plaque radiotherapy by Oosterhuis in 1995.\textsuperscript{218} TTT has been used in combination with plaque therapy\textsuperscript{219} is also known as sandwich
therapy.\textsuperscript{220} Some investigators have subsequently used TTT as a primary treatment for small (less than 4 mm in height) choroidal melanomas.\textsuperscript{221}

Using a modified 810 nm wavelength diode laser and a contact lens, 2 to 3 mm confluent burns are delivered for one to two minutes over the tumour and around a 1 mm margin through a dilated pupil via a slit lamp biomicroscope. Up to three applications are delivered, three to four months apart.\textsuperscript{221} The laser spots result in temperatures of 45 to 60 °C, causing immediate cell damage and tumour necrosis.\textsuperscript{222} Thermal penetration of the tumour reaches a maximum of 4 mm in depth.\textsuperscript{223} An atrophic chorioretinal scar forms over the following months at the site of the tumour.

Advantages of TTT include low cost, immediate tumour necrosis and regression, avoidance of radiation retinopathy, as well the ability to treat patients on an outpatient basis with local anaesthetic.\textsuperscript{222, 224} TTT has been used for tumours within 5 mm of the fovea or optic disc, where radiation would result in potential loss of vision. Contraindications to TTT include:\textsuperscript{145}

- Reduced visibility of the fundus due to media opacities, such as cataract
- Peripheral tumour location, precluding access to laser
- Reduced tumour pigmentation

Ideal candidates are monocular patients with a tumour near critical visual structures, patients who are unfit for surgery, and patients with advanced diabetic retinopathy.\textsuperscript{223} Complications include epiretinal membrane formation, retinal traction, detachment, vascular occlusion and absolute wedge-shaped scotoma.\textsuperscript{221} In a retrospective case series of 135 patients, 32% developed one or more complications, often with visual consequences.\textsuperscript{223} Interest in TTT as primary therapy for choroidal
melanoma was based largely on the assumption that it provided better visual outcomes than plaque radiotherapy. However, no significant difference was found in a retrospective case-matched comparative study that compared TTT or plaque with TTT or TTT and plaque radiotherapy.\textsuperscript{225}

Although studies initially were encouraging, concern mounted about the use of TTT as a primary treatment due to the emergence of reported high rates of recurrence and complications. Local recurrence rates are higher with longer follow-up, and vary from 8 to 56\%.\textsuperscript{221} In a non-comparative interventional case series of 256 patients, Shields et al calculated a mean of twenty-two months to local recurrence.\textsuperscript{224} Pooled data of ten published case series contained 602 tumours and 100 recurrences, excluding eighteen tumours that did not regress with TTT only (primary failures).\textsuperscript{221} A weighted mean tumour recurrence rate of 17\% was calculated with a median follow-up of thirty-seven months.\textsuperscript{221}

Melanoma cells may survive after intrascleral or episcleral TTT because the temperature increase in the sclera is lower than that in the tumour. This is because less heat from infrared radiation is absorbed in the non-pigmented sclera than in the pigmented tumour.\textsuperscript{220} Risk factors for local treatment failure are increased tumour bulk, juxtapapillary location and reduced tumour pigmentation.\textsuperscript{145} Given that tumour recurrence may be associated with metastasis, TTT as primary or sole therapy for small choroidal melanomas is not recommended.\textsuperscript{221} Although it is a minimally-invasive laser procedure, TTT as a primary therapy carries significant risk of morbidity and metastatic disease.\textsuperscript{223} It has however, been used widely as an adjunct to brachytherapy to improve local tumour control and has been used as a treatment for macular oedema.
CHAPTER 6
Aim and Methods

6.1 Study design

A retrospective review of all patients receiving stereotactic radiotherapy for uveal melanoma at Dunedin Hospital between July 2001 and December 2007 was completed. Cases were identified through the Oncology Department radiotherapy log. All cases with a diagnosis of choroidal or ciliary body melanoma were eligible for inclusion in the study. Clinical records of twenty patients were reviewed. These included patients referred from other tertiary centres who were not eligible for plaque brachytherapy, patients with large tumours who did not want an enucleation, and all consecutive patients living in the Otago Region. Cases were identified through the Oncology Department radiotherapy log. All cases with a diagnosis of choroidal or ciliary body melanoma were eligible for inclusion in the study.

Outcome measurements were (1) local tumour control, (2) visual acuity and (3) radiogenic side effects after fractionated linear accelerator-based stereotactic radiotherapy. Patient age, tumour size, location, and baseline visual acuity were recorded, as well as the presence of symptoms, history of previous cancer or diabetes, and past ocular history. Treatment dose and post-treatment visual acuity and any adverse effects noted at follow-up were also recorded. Information was sourced from clinical patient notes, radiotherapy log, and after writing to the primary ophthalmologist for patients who lived in other parts of New Zealand. These variables were noted on a data collection sheet (see Appendix), which was
then entered into an Excel spreadsheet. Data on ethnicity were retrieved from Dunedin Hospital records. In New Zealand, ethnicity is a measure of self-perceived cultural affiliation.226

6.2 Ethics approval

Formal ethics committee approval for data retrieval was gained from the Lower South Regional Ethics Committee (LRS/08/03/EXP – see Appendix 2).

6.3 Pre-treatment investigation and treatment planning

Patients who lived out of Dunedin arrived a week before their treatment and stayed a fortnight in total. All patients underwent a detailed history and examination from an ophthalmologist. Staging procedures to exclude metastatic disease were performed in all patients prior to treatment, including B-scan ultrasound, fundus photos, blood tests (complete blood count, liver enzymes), chest x-ray, and liver ultrasound scan. A radiation oncologist reviewed patients, and a pre-treatment CT scan of the head was performed to enable treatment planning.

The first step in treatment planning involved making a head-fixation device for the patient. A modified Gill Thomas Cosman frame (Radionics) was customized with the patient’s bite impression and occipital impression to completely immobilize the head (figure 6.1). Eye movement was continuously monitored during treatment planning and delivery. An eye monitoring system was created using a small charge-coupled device camera and fibre optic light source for fixation, which was integrated into the mask system in front of the eye being treated (figure 6.2). If the treated eye could not fix on the camera due to poor visual acuity, the camera was set in front of the other
Eye movements were monitored on a television screen positioned in the control room by a radiation oncologist during CT imaging as well as during treatment delivery. Control points on the eyelids, the medial and lateral canthi, as well as the reflection from the fixation light were marked on the screen. The radiation therapist immediately stopped treatment if the eye deviated from its primary position.

Figure 6. 1: Gill Thomas Cosman Frame showing bite and occipital impressions (images courtesy Dr Lyndell Kelly)

During CT image acquisition for treatment planning the patient was instructed to look at the fixation light. Fine-slice CT was performed, with 1 mm slices at 1.5 mm increments through the lesion itself, and above and below 1 mm at 3 mm increments (Figure 6.3). The goal of treatment planning was to cover the planning target volume with the 80% isodose while minimizing radiation exposure to vulnerable structures (lacrimal gland, optic disc, lens, skin surface). Contouring was based on a combination of CT images, fundal photographs and ultrasound scanning of the tumour (Figure 6.4). B-scan ultrasound (10 mHz) provided definition to within 0.5 mm.
All patients were treated stereotactically with a linear accelerator with 6 MV photon beams in ten fractions over five days. Radiotherapy was delivered to patients lying supine. Total dose ranged from 45 to 70 Gy.

Figure 6. 2: Eye monitoring system with closed-circuit television screen and fibre optic fixation light (courtesy Dr Lyndell Kelly)

Figure 6. 3 (left): Planning CT scan demonstrating right choroidal melanoma with gross target volume and planning target volume and brainstem outlined. Note the fixation device and camera in front of the right eye. Figure 6.4 (right): Treatment contour plan showing direction of radiation arcs (images courtesy of Dr Lyndell Kelly)
Oral dexamethasone was commenced in patients treated from May 2006 in an effort to minimize post-radiotherapy orbital inflammation. Patients were given 4 mg twice daily for ten days followed by a two-week tapering dose. One dose of intravitreal bevacizumab (1.25 mg in 0.05 mL) was also given to patients in the week before radiotherapy from 2006. This was to ameliorate the effect of VEGF release from irradiated melanoma cells. Patients were examined regularly post-treatment, at intervals dependent on symptoms and at the discretion of their treating ophthalmologist. Those living outside the Otago area were referred back to their primary ophthalmologist for follow-up.

6.4 Data management and analysis

TNM tumour size (see Figure 2.1)\textsuperscript{31} was determined based on tumour thickness and largest basal diameter as measured on B-scan ultrasound. COMS tumour size (see Table 2.1)\textsuperscript{49} was also established from B-scan measurements. TNM tumour staging was based on the Seventh TNM Edition (see Table 2.2).\textsuperscript{51} Tumour volume (cm\textsuperscript{3}) was calculated by the radiation oncologist from CT and ultrasound images and was summarized using mean and standard deviation.

For this study, best-corrected visual acuity was converted to logarithm of the minimal angle of resolution (logMAR) units before analysis. Visual acuities of counting fingers, hand movements, light perception and no perception of light were assigned values of 1.85, 2.3, 2.6, and 2.9 respectively.\textsuperscript{227, 228} Visual acuity was then converted back to Snellen acuity (table 6.1).
Table 6.1: Visual acuity conversion

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6.5 Outcome measures

The primary outcome was local control, defined as continuous tumour regression or stable disease. Secondary outcomes included visual acuity, adverse effects, and metastatic death.
CHAPTER 7

Results

7.1 Baseline characteristics

A total of twenty-seven patients (16 male, 11 female) were treated from July 2001 to December 2007. Mean age was sixty-one years (standard deviation 14, range 27 to 81 years) and 16 right and 11 left eyes were treated. Seventeen patients were symptomatic while ten were discovered incidentally. Three patients had a history of diabetes mellitus, two of which had their melanomas diagnosed at retinopathy screening.

Table 7.1 presents a summary of demographic and treatment details. Nineteen patients were referred from Otago and Southland District Health Boards and eight were from other districts. All patients identified their ethnicity as New Zealand European. Five patients had a visual acuity of 6/36 or worse in their fellow eye. Clinical evidence of metastatic disease was not found in any patients screened at presentation. Follow-up ranged from 3 to 104 months (median 14 months). Patients outside the Otago and Southland Region had more advanced disease than those who lived locally.
Table 7.1: Patient treatment data.

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<th>Final VA (Snellen)</th>
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Key: F = female, M = male, DHB = District Health Board, COMS = Collaborative Ocular Melanoma Study tumour size, S = small, M = medium, L = large (see Table 2.1), TNM = Tumour, Node, Metastasis staging (see Table 2.2), Gy = Gray, VA = visual acuity, Y = received treatment, HM = hand movements, NPL = no perception of light, LP = light perception, *final visual acuity before enucleation, DEAD UM = death due to metastatic uveal melanoma
Eight patients had a history of previous cancer. Case 12 (see Table 7.1) had previous Dukes B bowel cancer resected ten years before presentation. Case 13 underwent an orchidectomy for cancer, four years before presentation. Case 15 had a history of two cutaneous melanomas excised two years earlier, one on the hand and one on their head. Case 18 had a previous pituitary adenoma treated nineteen years before presentation with radiotherapy. Case 22 previously underwent radical radiotherapy for prostate cancer. Case 27 had a melanoma removed from her face as well as treated vulval carcinoma. Case 26 gave a history of low-grade T cell leukaemia, treated three years earlier and clinically in remission. Case 10 had a history of bilateral choroidal melanoma, which is reported in detail in Section 7.6.

Mean tumour volume was 0.61 cm$^3$ (standard deviation ±0.69). Tumours were located throughout the posterior uveal tract, at the posterior pole (9), equator (7), juxtapapillary (4), ciliary body (4), and macula (3). Using COMS sizing, there were twelve small, nine medium and six large tumours. TNM staging was also determined using tumour size data, and is displayed in the table above. Nine patients were given one dose of intravitreal bevacizumab (1.25 mg in 0.05 mL) in the week before SRT. Fourteen patients were given dexamethasone 4 mg twice daily from day one of SRT to day seven to control orbital oedema.

### 7.2 Local control and eye retention

Local control, with clinically stable or regressing tumour size, was achieved in all patients. Three patients in total underwent secondary enucleation after SRT. One patient (case 9) had a recurrent retinal detachment, making clinical examination of the tumour difficult, and the only means of monitoring tumour size was by ultrasound. Given that this eye had no vision, the decision to enucleate was made.
Case 5 had a recurrent vitreous haemorrhage precluding fundal view, and despite vitrectomy and endoresection, went on to have an enucleation due to continued vitreous cavity haemorrhage. Case 18 had his eye enucleated for intractable pain.

### 7.3 Visual acuity

Of the 24 patients who retained their eye at final follow-up, visual acuity deteriorated in eighteen (75%). Mean Snellen visual acuity of all patients at baseline was 6/24 (logMAR 0.64, \(\pm 0.97\)), dropping to 6/75 in the 24 patients who retained their eye at final follow-up (24 patients, logMAR 1.10, \(\pm 1.14\)). Median visual acuity similarly decreased from 6/6 (logMAR 0) to 6/21 (logMAR 0.55).

Cases 16, 18, and 24 had tumours involving their macula. Case 16 developed radiation retinopathy, treated with intravitreal bevacizumab and pan-retinal photocoagulation. Case 18 had his T3a tumour treated with a cumulative dose of 70 Gy. He had his eye enucleated for pain ten months later and died of metastatic disease six months after enucleation. Decreased vision in Cases 1 and 11 was due to cataract. Case 10 developed peripheral corneal thinning with dry eye.

Seven patients developed maculopathy, which limited their vision. Case 7 had atrophic age-related macular degeneration (ARMD) at baseline which continued to progress. Case 21 also had ARMD with a choroidal neovascular membrane. Cases 2, 13, 15, 19, and 23 developed ischaemic maculopathy. Case 2 presented with a T3b tumour at his ora, involving the ciliary body. He developed neovascular glaucoma, which was controlled on medical treatment, but went on to die of metastatic disease despite chemotherapy, sixteen months after SRT. Cases 13, 15 and 19 also developed dry eye symptoms. Case 15 and 19 underwent cataract extractions. Case 23 had a
juxtapapillary T1a tumour and developed optic neuropathy in addition to ischaemic maculopathy.

Nine patients presented with exudative retinal detachments and in four patients these became chronically detached. Case 8 presented with a large T4b tumour involving the ciliary body in his only eye. He developed a chronic total retinal detachment with rubeosis and a normal intraocular pressure. He then underwent an endoresection with debulking of the treated tumour, followed by cataract extraction and pars plana vitrectomy with silicone oil. Case 9 had an enucleation for chronic exudative detachment fifty weeks after SRT. Case 20 had a total exudative detachment with “kissing retina” at last follow-up. Case 22 also developed a total exudative retinal detachment with cataract.

Two patients developed non-clearing vitreous haemorrhages. Case 5 underwent a vitrectomy and trans-scleral local resection but his eye was subsequently enucleated due to recurrent haemorrhage. Case 17, seventy-five years old, had type one diabetes mellitus with moderate non-proliferative diabetic retinopathy pre-treatment. She developed bilateral vitreous haemorrhages despite pan-retinal photocoagulation.

7.4 Radiation-related side effects

A total of eight patients had documented radiation retinopathy, involving the macula in five patients as described above. Two patients developed neovascular glaucoma (cases 2 and 8), and case 23 developed optic neuropathy. In general, these patients had worse visual outcomes. Four patients had significant dry eye symptoms (cases 10, 13, 15 and 24). Cataract was documented in five cases (1, 10, 15, 19, 22).
7.5 Metastatic death

Ten patients were known to have died by final follow-up, of which the cause of death was known for four patients. Case 23 died of metastatic bowel cancer, and three others (cases 2, 10, 18) were known to have died of metastatic uveal melanoma at final follow-up.

7.6 Case report

Case 10 - a fifty-three year-old male - was initially referred in 1998 by his optometrist who noted conjunctival pigmentation. This had been present for twenty years. The patient had bilateral oculodermal melanocytosis, with slate grey pigment in the episclera, both superiorly and inferiorly. A small amount of skin around the left lower punctum was also affected. His medical history included myopia, ischaemic heart disease and elevated cholesterol.

In 2001 he presented with reduced left visual acuity of 6/12 due to a left non-ischaemic infero-temporal branch retinal vein occlusion (BRVO) with mild macular oedema. Initially, a raised grey mass was noted in the left nasal fundus, measuring 8.0 mm wide and 3.5 mm thick with ultrasonography. He had no evidence of metastatic disease. Given the location of the melanoma and the presence of a left BRVO it was felt that trans-pupillary thermotherapy (TTT) would be an appropriate treatment. He underwent three courses of TTT over six months and his lesion responded to treatment. A year later he was diagnosed with a right supero-temporal choroidal melanoma. It was contiguous with the ciliary body, measuring 4.6 mm in height on ultrasound.
scan with a basal diameter of 9.2 mm. Visual acuities were 6/7.5 right and 6/18 left. He was treated with iodine-125 brachytherapy.

Two years later, having developed an epiretinal membrane, he underwent a left vitrectomy and epiretinal membrane peel, and corrected visual acuity improved from 6/30 to 6/15. The following year he underwent bilateral cataract extractions. In 2007 he was noted to have a raised pigmented lump supero-temporally on the external right globe, with some hollowing out on the inside, where the right choroidal melanoma (treated with radioactive iodine plaque) had been located. Fundus examination, B-scan and MRI scan found no evidence of any residual solid tumour.

The patient was followed at six-monthly intervals. In 2008, a year after an MRI scan, sentinel vessels were found on the external surface of the right eye and an inferior ciliary body melanoma was present with an apical thickness of 10.5 mm on ultrasonography. This was non-contiguous with the previous supero-temporal lesion. He was referred for fractionated stereotactic radiotherapy and received 50 Gy in five fractions over a week. Six arcs were used over a wide field.

The patient then developed severe external eye disease with bilateral involvement of the meibomian glands as well as peripheral corneal thinning. A staging CT scan of his eye and orbit was performed three months after radiotherapy. This showed a suspicious area of soft tissue opacification in the infero-medial quadrant of the right
orbit, which possibly represented extra-scleral extension or metastasis of the melanoma. Ultrasound scan of his liver revealed a solitary metastasis. The patient died four months later at the age of sixty-three, seven years after the diagnosis of his first tumour.
CHAPTER 8
Discussion

8.1 International data

This study was a retrospective audit of the first cohort of patients with ciliary body and choroidal melanoma treated in New Zealand with fractionated SRT. Stereotactic radiotherapy for the treatment of uveal melanoma is a relatively new procedure. Case series of Linac-based SRT have been reported in the literature from Austria,\textsuperscript{229} the Netherlands,\textsuperscript{231} Canada,\textsuperscript{232, 233} Japan,\textsuperscript{234} Germany,\textsuperscript{235} China\textsuperscript{236} and Spain.\textsuperscript{237} Table 8.1 summarizes the findings from the international literature. The largest series published is from the Vienna University group, with up to ten years of follow-up.\textsuperscript{230} They treated 212 patients with choroidal melanoma according to a prospective protocol if they were unsuitable for brachytherapy with ruthenium-106 or local resection. Initial tumour height was at least 7 mm, or more than 2.5 mm in cases of juxtapapillary or juxtamacular tumours. The first 24 patients received a total dose of 70 Gy to the 80% isodose, which was reduced to 60 Gy for the next 158 patients, and further reduced to 50 Gy for subsequent patients. They found no significant difference in outcomes, although follow-up in the 50 Gy cohort was shorter. They did find that the time for visual acuity to drop below 0.1 was faster in the 70 Gy group (which had 14 Gy fractions) compared to the lower doses. There were 39 enucleations (18\%) during the follow-up period, and the most frequent causes of enucleation were neovascular glaucoma (25 cases) and recurrent tumour growth (8
cases). The majority of patients had a decrease in vision. Tumours near the macula and close to the optic disc have a worse visual prognosis and higher risk of local recurrence, which was reflected in their findings. They concluded that their local control rates were similar to proton therapy.

Another prospective longitudinal cohort study has been reported from the Netherlands. A total of 102 patients with choroidal or ciliary body melanoma were prospectively evaluated at a single institution. Tumours were 12 mm thick or less with a diameter less than 16 mm. A total dose of 50 Gy was delivered in 10 Gy fractions on five consecutive days. Follow-up was relatively short with a median of 32 months (range 2-92). Fifteen enucleations were performed (15%), mainly for neovascular glaucoma (8) and progression (4).

A retrospective review from Montreal reported on 50 consecutive patients with juxtapapillary choroidal melanoma (tumours within 2 mm of the optic disc). Most patients had 60 Gy delivered in 10 fractions over two weeks. A similar series in Toronto delivered higher doses of 70 Gy in five fractions. This study compared SRT with iodine-125 brachytherapy and found that SRT had higher radiation-induced comorbidities at four years. There was no mention of visual acuity outcomes but an earlier case series from the same institution looked at 28 patients with juxtapapillary choroidal melanoma. These were treated with 70 Gy in five fractions over ten days and found initial median Snellen acuity at 20/100, which dropped to counting fingers vision at 18 months.

An older case series from Japan presented 16 patients with choroidal melanoma of heterogenous size and location. The first eight patients received hyperthermic treatment to the surface of the cornea in an attempt to heat the melanoma and make
it more radiosensitive. A range of SRT doses were given and follow-up was relatively short. A group in Germany studied SRT of choroidal tumours – both melanomas and choroidal metastases.\textsuperscript{235} The melanoma group comprised ten patients who were treated with either 12-20 Gy in one fraction or 30 Gy in 10 fractions.

A group in Spain evaluated a technique of eye immobilization by eyelid closure during SRT.\textsuperscript{237} They treated five patients with choroidal melanoma in this way and recommended safety margins of 3 mm for this technique. A report from China described 16 patients with choroidal melanoma who were given a range of doses.\textsuperscript{236} Two patients had single doses of 35 Gy and 25 Gy and the remaining patients had 30-55 Gy in 2-4 fractions over 4-16 days. Seven patients underwent enucleation for neovascular glaucoma (3), tumour growth (2) and corneal ulcer (2). At final follow-up (median 66 months) “all were blind, all were alive”.
Table 8.1: Comparison of international data of stereotactic radiotherapy of uveal melanoma

<table>
<thead>
<tr>
<th>First author City Year</th>
<th>Number of patients</th>
<th>Fractions (n)</th>
<th>Total dose (n)</th>
<th>Median follow-up (months)</th>
<th>Local control</th>
<th>VA baseline</th>
<th>VA follow-up</th>
<th>Eye retention</th>
<th>Metastasis-free survival</th>
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<tbody>
<tr>
<td>Dunavoegyi Vienna 2011</td>
<td>212</td>
<td>5</td>
<td>70 Gy (24) 60 Gy (158) 50 Gy (30)</td>
<td>64.5</td>
<td>95.9% (5-yr) 92.6% (10-yr)</td>
<td>0.55</td>
<td>HM</td>
<td>78.6% (5-yr) 72.6% (10-yr)</td>
<td>85% (5-yr) 75% (10-yr)</td>
</tr>
<tr>
<td>Muller Rotterdam 2012</td>
<td>102</td>
<td>5</td>
<td>50 Gy</td>
<td>32</td>
<td>96%</td>
<td>0.26</td>
<td>0.03 (4-yr)</td>
<td>85%</td>
<td>75% (5-yr)</td>
</tr>
<tr>
<td>Krema Toronto 2013</td>
<td>64</td>
<td>5</td>
<td>70 Gy</td>
<td>46</td>
<td>93% (4-yr)</td>
<td>Not stated</td>
<td>Not stated</td>
<td>90% (4-yr)</td>
<td>74% (4-yr)</td>
</tr>
<tr>
<td>Al-Wassia Montreal 2011</td>
<td>50</td>
<td>9 (3) 10 (47)</td>
<td>54 Gy (3) 60 Gy (47)</td>
<td>29</td>
<td>86% (5-yr) 1.0 (18%) &lt;0.1 (40%)</td>
<td>&lt;0.1 (66%)</td>
<td>94%</td>
<td>78.6% (5-yr)</td>
<td></td>
</tr>
<tr>
<td>Tokuuye Tokyo 1997</td>
<td>16</td>
<td>8 (14) 5 (1) 9 (1)</td>
<td>48 Gy (14) 30 Gy (1) 54 Gy (1)</td>
<td>Range 8-46 months</td>
<td>94%</td>
<td>Not stated</td>
<td>Not stated</td>
<td>87.5%</td>
<td>Not stated</td>
</tr>
<tr>
<td>Bellman Heidelberg 2000</td>
<td>5</td>
<td>10 (4) 5 (1)</td>
<td>50 Gy</td>
<td>6.5</td>
<td>100%</td>
<td>Median 0.4</td>
<td>Median 0.25</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>This study</td>
<td>27</td>
<td>5</td>
<td>50 Gy (24) 70 Gy (1) 60 Gy (1) 45 Gy (1)</td>
<td>14</td>
<td>100%</td>
<td>0.25</td>
<td>0.08</td>
<td>89%</td>
<td>89%</td>
</tr>
</tbody>
</table>

Key: Gy = Gray, HM = hand movements, yr = year
8.2 Radiation dose

Uveal melanoma is known to be radioresistant, and high radiation doses are required to treat tumours. Most patients (24/27) in this audit received a total dose of 50 Gy to the 80% isodose line surrounding the tumour with a 2 mm margin as planning target volume. The first three patients received a total dose of 45 Gy, 70 Gy and 60 Gy respectively. It is interesting to note that a number of centres reduced the radiation dose in their treatment regimes over time to minimize radiation-related side effects. The Vienna group found no significant difference in outcomes for 50-60 Gy groups, but those treated with 70 Gy tended to drop visual acuity faster than those treated with lower doses.\textsuperscript{229}

Given that high doses are required for local tumour control, it is inevitable that surrounding structures get relatively high radiation doses in the area around the planning target volume. In this study of twenty-seven patients, radiation retinopathy was documented in eight cases, optic neuropathy in one case, and cataract in five cases. The two patients who developed neovascular glaucoma had the largest tumours of the group – T3b (case 2) and T4b (case 8). The Vienna group found that largest tumour diameter was an important prognostic factor for radiogenic side effects, and that optic neuropathy and radiation maculopathy were increased by virtue of the fact that these tumours were posteriorly located.\textsuperscript{229}

8.3 Eye retention

Eye retention is one of the main advantages of SRT, however secondary enucleation may be performed if local control fails or significant tumour- or radiation-related side effects occur. Three of twenty-seven patients (11%) underwent secondary
enucleation after median follow-up of fourteen months in this study, for recurrent vitreous cavity haemorrhage (case 5, Table 7.1), recurrent retinal detachment (case 9, Table 7.1), and intractable pain (case 18, Table 7.1). Table 8.2 outlines reasons for enucleation from international data. The most common cause for enucleation was neovascular glaucoma, followed by tumour growth.

Table 8.2: Reasons for enucleation post SRT

<table>
<thead>
<tr>
<th>First author City</th>
<th>Enucleation rate</th>
<th>Enucleation %</th>
<th>Reason for enucleation (number)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Neovascular glaucoma Growth</td>
</tr>
<tr>
<td>Dunavoelgyi Vienna</td>
<td>39/212</td>
<td>18</td>
<td>25 8 3 2 1</td>
</tr>
<tr>
<td>Muller Rotterdam</td>
<td>15/102</td>
<td>15</td>
<td>8 5 1 1 1</td>
</tr>
<tr>
<td>Krema Toronto</td>
<td>6/64</td>
<td>9</td>
<td>4 2</td>
</tr>
<tr>
<td>Al-Wassia Montreal</td>
<td>3/50</td>
<td>6</td>
<td>1 1 1</td>
</tr>
<tr>
<td>Tokuuye Tokyo</td>
<td>2/15</td>
<td>13</td>
<td>1 1</td>
</tr>
<tr>
<td>This study</td>
<td>3/27</td>
<td>11</td>
<td>1 1</td>
</tr>
<tr>
<td>Total</td>
<td>68/470</td>
<td>14%</td>
<td>39 17 3 3 3 1 1 1</td>
</tr>
</tbody>
</table>
Fernandes et al in Toronto documented ten eyes with juxtapapillary choroidal melanoma treated with SRT doses of 70 Gy (in 5 fractions over 10 days) were enucleated due to neovascular glaucoma (6) and tumour progression (4).\textsuperscript{239} Retinal damage and radiation-induced retinal vascular changes were more prominent in the NVG group and there were no features of radiation damage in the anterior chambers, leading researchers to conclude that NVG is due to radiation damage in the posterior of the eye rather than primary damage to anterior segment structures.\textsuperscript{239}

A retrospective study from the Netherlands analysed 118 consecutive patients treated with fractionated SRT for choroidal and ciliary body melanoma.\textsuperscript{240} Median follow-up was 4.7 years, during which time 19 patients (16\%) underwent secondary enucleation. Six were due to failure of local tumour control (5\%), 12 due to neovascular glaucoma and one due to diffuse radiation retinopathy. They found that the overall risk of secondary enucleation following SRT increased significantly with tumour height.

The Collaborative Ocular Melanoma Study reported on secondary enucleation following iodine-125 brachytherapy.\textsuperscript{241} A total of 650 patients received brachytherapy, and 85 patients underwent enucleation (13\%). They reported a 12.5\% rate of secondary enucleation within five years of treatment. Half of patients were enucleated due to failed local control and the remainder were due to pain and poor vision. Histopathological analysis found that 55\% of eyes had vascular abnormalities suggestive of radiation retinopathy.
8.4 Visual acuity

The lens, macula and optic nerve are critical parts of the visual pathway that are vulnerable to radiation damage. The lens is the most radiosensitive ocular structure, and has no threshold radiation dose for cataract formation.\textsuperscript{216} Cataract extraction is usually straightforward and reverses lens-related visual impairment, however ischaemic radiation retinopathy and optic neuropathy can be very difficult to treat.

It has been widely noted that visual acuity decreases post-radiotherapy and a number of factors account for this. Tumours at the posterior pole are close to the macula and optic nerve and by virtue of their location become susceptible to collateral radiation-induced ischaemia. In this study, visual acuity decreased in three-quarters of patients who retained their eye (18 of 24 patients), with median Snellen acuity dropping from 6/6 to 6/21.

8.5 Study strengths

All patients who were treated with SRT in Dunedin within the 7.5-year period were included in this study, and clinical notes could be located for all patients.

8.6 Study limitations

By virtue of the retrospective nature of this study, information was limited to that data recorded in clinical notes. Side-effects not recorded may not have been specifically asked about, or may have not been deemed sufficiently significant for the doctor to record. Visual acuity was converted from Snellen scores at six metres and four metres recorded in different hospitals to the logMAR equivalent. B-scan is also
operator-dependent and not all patients had their scans done in the same hospital by the same radiologist.

The treatment regime evolved over the course of the audit period. The radiotherapy dose changed with the first three patients receiving a total dose of 45, 70, and 60 Gy respectively, and the following 24 patients receiving 50 Gy. Dexamethasone was introduced to control orbital inflammation, and intravitreal bevacizumab was administered prior to radiotherapy from 2006. Due to small numbers, this study has insufficient power and it is difficult to measure the effect of these interventions.

8.7 Case study

We reported the case of a patient with oculodermal melanocytosis with two uveal melanomas in one eye and another uveal melanoma in the opposite eye. This is a very rare occurrence and illustrates the inadequacy of our current diagnosis and treatment of this cancer – metastatic disease often occurs before the primary tumour is diagnosed.

8.8 Conclusions

Uveal melanoma is a rare disease and it is very difficult to conduct an adequately powered study in the New Zealand population. This retrospective audit supports international literature that fractionated stereotactic radiotherapy is a useful addition to the range of eye-sparing treatment for uveal melanoma.

Randomized controlled trials that are underpowered do not adequately test the underlying hypothesis and are considered by some as scientifically useless and
Therefore unethical. However, an underpowered trial could be justified if the authors explicitly plan to combine their prospective trials with other similar ones with comparable research methods for a prospective multicentre meta-analysis.

8.9 Future directions

This study has shown that SRT for the treatment of uveal melanoma is an area worthy of further research. Since data on this cohort was collected, there have been no major changes to the management of patients undergoing SRT for uveal melanoma. A national ocular cancer database with patient information could be established to accrue larger patient numbers and enable ongoing audit and prospective studies. Areas for further research include quality-of-life, cost-benefit analyses, dose fractionation, treatment response as a function of tumour gene analysis, and the role of adjunctive steroid therapy and intravitreal bevacizumab.
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### Appendix 1: Data collection sheet

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<tr>
<th><strong>STEREOTACTIC RADIOTHERAPY OF UVEAL MELANOMA - DUNEDIN 2001-2007</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dr Genevieve Oliver, Professor Anthony CB Molteno, Dr Lyndell Kelly</strong></td>
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<table>
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<tr>
<th><strong>Type of Cancer</strong></th>
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<td>Age</td>
<td>Date</td>
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<td>Lipofuscin</td>
<td>Serous Ret Detachment</td>
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<td>Fovea</td>
<td>Pre-Equatorial</td>
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<td><strong>BCVA / IOP at diagnosis</strong></td>
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<td>Abdo USS</td>
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<td><strong>Metastasis?</strong></td>
<td>Y / N</td>
<td>Y / N</td>
<td>Y / N</td>
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<tr>
<td><strong>Death - cause / date</strong></td>
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<td><strong>Ocular comorbidities affecting VA</strong></td>
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<tr>
<td><strong>XRT Complications</strong></td>
<td>New cataract</td>
<td>Radiation Retinopathy</td>
<td>Neovascular Glaucoma</td>
<td>Optic Neuropathy</td>
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<tr>
<td><strong>Others (specify)</strong></td>
<td></td>
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<tr>
<td><strong>Further Treatment</strong></td>
<td>Plaque</td>
<td>Enucleation</td>
<td>Other</td>
<td></td>
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<tr>
<td><strong>Dates / Reason</strong></td>
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<td><strong>Further comments</strong></td>
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</tbody>
</table>

Appendix 1 – Patient data sheet. BCVA = best-corrected visual acuity, IOP = intraocular pressure, PSCO = posterior subcapsular opacity, CXR = chest x-ray, USS = ultrasound scan, GTV = gross target volume, DD = disc diameters, VA = visual acuity, XRT = radiotherapy
Appendix 2: Ethics Approval Forms

Lower South Regional Ethics Committee
Ministry of Health
228 Monr Place
PO Box 549
Dunedin
Phone (03) 474 8562
Fax (03) 474 8080

5 March 2008

Dr Genevieve Oliver
Ophthalmology Section
University of Otago
PO Box 13
Dunedin

Dear Genevieve,

Project Key: LRS/08/03/EXP
Full Title: Stereotactic radiotherapy of uveal melanoma: The NZ experience.
Investigators: Dr. Genevieve Oliver, Professor Anthony CB Molteno, Dr. Lyndell Kelly.
Locallities: Eye Clinic, Dunedin Hospital

The above study has been given ethical approval by the Lower South Regional Ethics Committee.

Progress Reports
The study is approved until 31 March 2009. The Chairperson will review the approved application annually and notify the Investigator if they withdraw approval. It is the Investigator’s responsibility to forward a progress report prior to ethical review of the project in 5 February 2009. The report form is available on http://www.newhealth.govt.nz/ethicscommittees. Please note that failure to provide a progress report may result in the withdrawal of ethical approval. A final report is also required at the conclusion of the study.

Amendments
It is also a condition of approval that the Committee is advised if the study does not commence, or is altered in any way, including all documentation eg advertisements, letters to prospective participants.

Please quote the above ethics committee reference number in all correspondence.

It should be noted that Ethics Committee approval does not imply any resource commitment or administrative facilitation by any healthcare provider within whose facility the research is to be carried out. The organisation may specify their own processes regarding notification or approval.

Yours Sincerely,

Riria Tautau-Grant
Ethics Committee Administrator
Lower South Regional Ethics Committee
email: riria_tautau-grant@moh.govt.nz

6/05/2008

Prof Tony Molteno
Ophthalmology,

REF: Experience with Stereotactic Radiotherapy for Choroidal Melanomas at Dunedin Hospital

Dear Prof Molteno

I am writing on behalf of the combined Otago District Health Board and Dunedin School of Medicine, Research Advisory Group to confirm that the project mentioned above has been granted approval to proceed.

According to my records:
This project is due to commence: 6/5/2008
It should be complete by: 31/03/2009

If you have any questions with regards to this project please contact me quoting the project ID shown above.

Yours sincerely

[Signature]

Ali Cameron
Clincial RESEARCH ADVISOR

CC COLLEEN COOP, ODHb
Genevieve Oliver, OPHTHALMOLOGY REGISTRAR

Health Research Office
Otago District Health Board
Internal Mail Box #22
201 Great King Street
DUNEDIN

Phone DDI 474 7708 extn 5085
ali.cameron@otago.ac.nz

Dunedin School of Medicine
The Deans Office
University of Otago
P.O. Box 913
DUNEDIN