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Brachytherapy and Endoresection in the  
Treatment of Choroidal Melanoma.  
A review of patients treated in South Africa

Minor dissertation

Submitted in partial fulfilment of the degree of Masters of  
Public Health (Clinical Research)

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RCXJAM002

**Submitted February 2012**

## **Abstract**

### **Study aims:**

This study is a retrospective cohort analysis of patients undergoing two different treatment modalities (brachytherapy and endoresection) for medium sized choroidal melanoma. Study methods involve the collection of baseline and follow-up data from three sources: 1) A database collected by the department of Radiation Oncology at Groote Schuur Hospital; 2) Private physicians responsible for patient follow-up following brachytherapy; 3) Private physicians responsible for endoresection surgery and patient follow-up. To date there has been limited publication of the outcomes of patients treated for choroidal melanoma in South Africa. The study aims to compare the outcomes of these procedures to help identify the possible benefits of each form of treatment.

### **Literature search:**

The literature review reveals a paucity of comparative studies of these treatment methods. Most publications are case series and meta-analyses. Useful comparative information can be obtained from the Collaborative Ocular Melanoma Study which was designed to compare conservative (eye preserving) treatment with enucleation (removal of the eye). The outcome of patients treated with brachytherapy in this study is a useful reference but no comparison was made with other forms of conservative treatment such as endoresection.

**Findings:**

We found that brachytherapy had 4.2 times increased risk of poor visual outcomes compared to endoresection. Mean visual acuity of eyes with vision better than perception of light (PL) was similar between the groups and approximately 40% of each group had good visual outcomes. The tumours that underwent endoresection were taller and further from the fovea than those receiving brachytherapy which may represent a selection bias. The numbers in the endoresection group were also small which limited the power of the study. Predictors of poor vision, recurrence rates, enucleation rates and metastases or death were similar to other published results.

**Further analysis:**

Data quality and loss to follow-up are discussed separately. In addition it was noted during the study that patients treated with brachytherapy prior to 1<sup>st</sup> May 1994 received sub therapeutic doses of radiation. These patients were analysed as a group and revealed significantly poorer outcomes compared to those treated with brachytherapy after 1<sup>st</sup> May 1994.

## **Acknowledgements**

### **Associate Professor Landon Myer (Supervisor)**

Infectious Diseases Epidemiology Unit, School of Public Health & Family Medicine, University of Cape Town, Cape Town, South Africa & Department of Epidemiology, Mailman School of Public Health, Columbia University, USA.

### **Professor Colin Cook (Co-supervisor)**

Department of Ophthalmology, Groote Schuur Hospital, Observatory, Cape Town, South Africa.

### **Dr Karin Lecuona**

Department of Ophthalmology, Groote Schuur Hospital, Observatory, Cape Town, South Africa.

Dr Lecuona presently oversees the management of all ocular tumours at Groote Schuur Hospital. I am grateful for her guidance, advice and support.

### **Dr Raoul Scholtz**

Private Practice. Melrose House, 14 Palmyra Road, Claremont, 7708, Cape Town. For his support and insights as well as contribution of endoresection data.

### **Professor Claire Stannard**

Department of Radiation Oncology, Groote Schuur Hospital, Cape Town, South Africa.

For unlimited access to the database of eye patients treated with brachytherapy in the department of Radiation Oncology, Groote Schuur Hospital. This database included patient information and tumour characteristics at the time of treatment.

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## DECLARATION

MPH Course Code: Minor Dissertation

Assignment Title: Brachytherapy and Endoresection in the Treatment of Choroidal Melanoma. A review of patients treated in South Africa

I JAMES RICE Student No. RCXJAT002  
declare that the work that I have submitted is my own and where the work of others has been used (whether quoted verbatim, paraphrased or referred to) it has been attributed and acknowledged.

Signature: \_\_\_\_\_

Signed by candidate

Date: FEBRUARY 2012

**Brachytherapy and Endoresection in the Treatment of Choroidal Melanoma.**

**A review of patients treated in South Africa**

Minor dissertation

Submitted in partial fulfilment of the degree of Masters of Public Health (Clinical Research)

**James C. Rice**

**RCXJAM002**

**Changes/corrections made to the dissertation**

**PART A PROTOCOL**

Typing errors corrected.

Additional information included (pg 6-7) on accuracy of correct diagnosis of tumour recurrence.

**PART B LITERATURE REVIEW**

Clarification provided regarding definition of tumour thickness (Table 1)

Further information included about physical properties of Ruthenium106 and Iodine125 brachytherapy. Page 3

Discussion of visual loss in patients receiving brachytherapy included with references. Page 5

Discussion on management of radiation maculopathy included with references. Page 5

Further discussion included on the importance of monosomy 3 and gains on chromosome 8 in the genetics of choroidal melanoma. Page 8

Further clarification of the role of brachytherapy in patients receiving endoresection. Page 11-12

Additional references included. Page 17

Typing errors corrected

**PART C MANUSCRIPT**

Further discussion on visual loss in both treatment groups included. Page 4

Clarification made about the comparison of visual outcomes in our study and the Collaborative Ocular Melanoma Study (COMS). Page 12

Further clarification regarding visual trends. The analysis of these trends was not possible because of study design. Page 13

Clarification on the role of consolidation treatment and patient numbers included. Page 13

Clarification regarding loss to follow-up. Loss to follow-up was only differential with respect to age and not with respect to procedure performed. It is thus less likely to represent bias. Page 15

Typing errors corrected

**APPENDIX E**

Typing errors corrected

**APPENDIX F**

Table A amended (percentages removed)

**APPENDIX H**

Logistic regression analysis for patients treated prior to 1<sup>st</sup> May 1994 –  
Table clarified and changed

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## **PART A: PROTOCOL**

### **Title:**

Brachytherapy and Endoresection in the Treatment of Choroidal Melanoma.

A review of patients treated in South Africa

### **Summary:**

This retrospective cohort study aims to assess the outcomes of patients with medium sized choroidal melanomas treated with brachytherapy or endoresection and to make comparison of the outcomes following these treatments.

Data to be obtained from three sources:

- 1) Pre-operative patient and tumour characteristics collected by the department of Radiation Oncology at Groote Schuur Hospital.
- 2) Follow-up data from private physicians responsible for patient follow-up following brachytherapy.
- 3) Pre- and post-operative data from private physicians responsible for endoresection surgery and patient follow-up.

Pre-operative data include age, gender, date of diagnosis, left or right eye, pre-operative visual acuity, presence of other non-associated pathology and type and date of the procedure performed.

Documented pre-operative tumour characteristics include height (thickness), largest basal diameter, distance from the optic disc, fovea and limbus, location within the

eye (predominant quadrant), and the presence or absence of an associated exudative retinal detachment.

Outcomes to be measured are duration of follow-up, final best corrected visual acuity and complications related to the tumour or treatment, particularly: 1) Recurrence of the tumour and date of recurrence; 2) Enucleation and the date and reason for enucleation; 3) Date of diagnosis of metastases or death from any cause.

Rates of tumour recurrence, enucleation and metastases will be calculated for each treatment group. Survival type analysis will be performed on both treatment groups with events being recurrence, enucleation and metastases or death from any cause. Comparison of treatment outcomes between the two treatment groups will be made. Risk factors of interest will be analysed in logistic regression and Cox proportional hazards models to determine possible predictors of outcomes.

**Rationale:**

Uveal melanoma is a rare condition that is managed in selected specialist centres. Groote Schuur Hospital is the only centre in South Africa to provide brachytherapy for the treatment of uveal melanoma. Patients are referred for treatment from private and public facilities throughout the country.

A database of patients undergoing brachytherapy for choroidal melanoma has been collected by the department of Radiation Oncology since 1974. This database is representative of the national experience of brachytherapy for choroidal melanoma.

To date only a small series of 21 patients was published in 1992<sup>1</sup>. It is the intention of this study to examine the outcomes of all patients with medium sized melanoma treated at this facility with brachytherapy. These outcomes will be compared to a national cohort of patients undergoing alternative treatment, namely endoresection.

Endoresection is a technically challenging surgical treatment for choroidal melanoma. It is performed by experienced vitreoretinal surgeons and the numbers in published series are small. The relatively small number of surgeons performing the procedure provides opportunity to gather data representative of the national experience of this form of treatment. This study will therefore provide a useful analysis and comparison of outcomes of the major forms of treatment used in South Africa for the management of choroidal melanoma. At present there are no similar studies from South Africa.

**Objectives:**

This study aims to assess the following outcomes of brachytherapy and endoresection in the treatment of uveal melanoma: final best corrected visual acuity; local tumour recurrence rate and time to recurrence; enucleation rate (removal of the eye) and time to enucleation; rate of metastases or death and time to diagnosis of metastases or death from any cause. Further analysis will explore baseline patient and tumour characteristics as predictors of these outcomes.

## **Methodology:**

### **Design**

This is a retrospective cohort study of two groups of participants, one undergoing brachytherapy and the other endoresection for the treatment of medium sized choroidal melanoma.

### **Subjects**

**Brachytherapy group:** All participants undergoing brachytherapy for this condition in South Africa have been treated at Groote Schuur Hospital or a nearby private facility with the use of a radioactive plaque supplied by Groote Schuur Hospital. A database was established in 1974 and will provide a list of consecutive participants who have undergone this procedure. As this form of treatment is most suitable for small or medium sized melanomas and most internationally published literature examines the outcomes of brachytherapy for medium sized tumours, participants with large tumours will be excluded from the analysis.

**Endoresection group:** Endoresections are performed by a select group of vitreo-retinal surgeons in the country. All members of the South African Vitreo-Retinal Society (SAVRS) will be contacted via the society email list inviting participation in the study (see Appendix B). Specific email notification will be sent to all surgeons with known experience in this procedure informing them of the proposed data collection and requesting their contribution to the database. More anterior tumours and large tumours are less amenable to endoresection and will be excluded from comparative analysis. Analysis of the endoresection group will be limited to primary

endoresections. Participants who have had prior treatment to the tumour and had a subsequent (secondary) endoresection will be excluded.

### **Interventions:**

#### ***Brachytherapy***

Brachytherapy is a form of radiation therapy applied via a custom made gold plaque inlaid with Iodine-125 radio-active seeds. Precise measurements of the size and location of the tumour are determined by a specialist ophthalmologist with particular reference to basal diameters and height (thickness) of the tumour, and its location within the eye with reference to the optic disc, fovea and limbus (sclera-corneal junction).

Manufacture of the plaque is overseen by a nuclear physicist in the department of Radiation Oncology at Groote Schuur Hospital. The plaque is sutured to the sclera overlying the tumour and remains in place for up to 5 days to achieve a therapeutic dose of 80-100Gy to the apex of the lesion.

#### ***Endoresection***

Endoresection is a surgical procedure in which the tumour is excised from the inner surface of the eye. The procedure is technically challenging and carries risk of significant complications. The eye is usually filled with silicone oil at the end of the procedure which remains for a period of at least 3 months to allow for stabilisation and healing of the surgical site. The risk of intra-operative complications is higher than with brachytherapy but visual outcomes may be superior for certain tumours.

**Observations:**

**Baseline observations** will include age, gender, date of diagnosis, left or right eye, pre-operative visual acuity, presence of other non-associated pathology and type and date of the procedure performed. Pre-operative tumour characteristics to be measured are height (thickness), largest basal diameter, distance from the optic disc, fovea and limbus, location within the eye (predominant quadrant), and the presence or absence of an associated exudative retinal detachment.

**Follow-up data:**

The most recent follow-up data available will be obtained on all participants. Follow-up of brachytherapy patients treated at our facility is performed by the referring ophthalmologist. Six monthly follow-up data are requested routinely from these ophthalmologists. If these updates are not available in the patient folder then it will be obtained from the referring practice by telephone and will be reliant upon accurate records being kept by the referring ophthalmologist.

In the case of endoresections, all baseline and follow-up data will be requested from the surgeon who performed endoresection.

Follow-up data will include best corrected final visual acuity and complications related to the tumour or treatment, namely: 1) Recurrence of the tumour and date of recurrence; 2) Enucleation of the eye and the date and reason for enucleation; 3) Date of metastases or death from metastases or any cause. Because Groote Schuur Hospital is the primary treatment centre for this condition, most cases of suspected

recurrence are discussed with specialists at this facility. This is likely to improve the accuracy of diagnosis of tumour recurrence.

Visual acuity may be recorded in different ways. Commonly used methods are Snellen acuity or decimal acuity. There are limitations to the use of these measures as they do not always give a good measure of overall visual function. Other measures of visual function are, however, not commonly measured in these patients. Snellen acuity and decimal acuity are not amenable to statistical analysis and will therefore be converted to logarithm of the minimal angle of resolution (LogMAR acuity) for analysis<sup>2</sup>. Visual measure of perception of light (PL) and no perception of light (NPL) are not truly measures of visual acuity but perception of a sensory stimulus and are not included in this scale<sup>2</sup>.

Below is a table relating different visual acuity measures:

**Table 1: Different visual acuity measures**

Snellen equivalent	Decimal equivalent	LogMAR equivalent
<b>6/6</b>	1.00	0.00
<b>6/12</b>	0.50	0.30
<b>6/18.9</b>	0.32	0.50
<b>6/37.5</b>	0.16	0.80
<b>6/60</b>	0.10	1.00
<b>Count Fingers (CF)</b>	0.01	2.00
<b>Hand Motions (HM)</b>	0.001	3.00

Recurrence of tumour growth is made on the basis of clinical examination and ultrasound measurements with comparison made with previous photographs and tumour dimensions. If an eye is enucleated it is possible to analyse the tumour histologically to confirm tumour recurrence.

Diagnosis of metastases is usually made with a combination of liver function testing, ultrasound of the liver and chest X-ray and confirmed by an oncologist. Screening investigations are usually performed six monthly in all patients that have been diagnosed with a uveal melanoma.

### **Sample size**

Endoresection is an uncommon, technically difficult form of treatment. We anticipate that numbers of participants receiving this treatment will be considerably fewer than those in the brachytherapy group. This may limit the power of statistical analysis to demonstrate differences in treatment outcomes.

### **Data management and analysis**

Data will be collected in a Microsoft Excel® database. Blank copies of the database will be emailed to all surgeons performing endoresection. Completed lists will be returned via email to Dr James Rice at james.rice@uct.ac.za who will collate and analyse the data.

STATA 11.0 (StataCorp. LP, USA) will be used to perform analysis. Mean and median outcomes will be used for normally and non-normally distributed data respectively except for mean of visual acuity and distances measured within the eye.

Visual acuity will be analysed in LogMAR format. As Perception of Light (PL) and No Perception of Light (NPL) are not measures of visual acuity but rather detection of a stimulus, they cannot be included in analysis of LogMAR acuities. Visual outcomes will therefore also be analysed categorically as follows:

- 1) Normal or mild visual impairment (6/5 to 6/18) (LogMAR -0.08 to 0.48)
- 2) Moderate visual impairment (6/24 to 6/48) (LogMAR 0.60 to 0.90)
- 3) Severe visual impairment (6/60 to 3/60) (LogMAR 1.00 to 1.30)
- 4) Profound visual impairment or blindness: 2/60 or worse (LogMAR 1.48 or worse)

PL and NPL vision will be ascribed a LogMAR value of 5 so as to be included in the blindness group for count purposes but will be omitted when determining the average visual acuity.

Risk factors for poor visual outcome will be examined in a logistic regression model using category 4 (profound visual impairment or blindness) as a dichotomous outcome variable. Presenting visual acuity and the type of treatment will be included in the model.

Survival type analysis will be performed on both treatment groups with events being recurrence, enucleation and metastases or death from all causes. Statistical comparison of survival curves will be made.

Risk factors of interest will be analysed in Cox proportional hazards models to determine their possible association with the outcomes. Regression model building will use Likelihood ratio tests and Aikaides information criteria (AIC) to determine the best model starting with a baseline of possible confounders.

### **Ethics**

Ethical approval for this study will be obtained from the University of Cape Town Faculty of Health Sciences Human Research Ethics Committee.

## References

(1) Hill JC, Sealy R, Shackleton D, Stannard C, Korrubel J, Hering E, et al. Improved iodine-125 plaque design in the treatment of choroidal malignant melanoma. *Br J Ophthalmol* 1992 02;76(2):91-94.

(2) Holladay JT. Proper method for calculating average visual acuity. *J Refract Surg* 1997 1997;13(4):388-391.

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## LITERATURE REVIEW

### Definition

Uveal melanoma is the most common primary intraocular malignancy in adults. The tumour is more common in Caucasians, with an overall incidence of 5-7 per million per year<sup>1,2</sup>. Known associations include ocular and oculodermal melanocytosis and other uncommon systemic conditions including neurofibromatosis type 1<sup>3,4</sup>.

The tumour arises from the pigmented cells of the uvea which is anatomically divided into the iris, ciliary body and choroid. This study will involve participants with choroidal melanoma only. Tumours can be classified according to size into small medium and large.

**Table 1: Classification of tumour size for the purpose of this study (varies slightly between studies)<sup>13</sup>**

	Height (thickness)	Largest basal diameter
<b>Small</b>	< 2.5mm	
<b>Medium</b>	2.5-10mm	≤ 16mm
<b>Large</b>	> 10mm	> 16mm

### Objectives of literature review

This review explores published outcomes related to the management of choroidal melanoma with brachytherapy and endoresection. Of interest are final visual acuity and rates of tumour recurrence, enucleation and metastases. Time to these events and risk factors for poorer outcomes are examined in the literature.

### Literature search strategy

A Medline search was performed using key words 'choroidal melanoma', 'brachytherapy', 'plaque therapy', 'radiotherapy', 'endoresection'. Outcomes of the treatment of large tumours and outcomes following secondary endoresections have not been reviewed.

### **Quality of included studies**

Because choroidal melanoma is an uncommon condition many publications are case series. Most series are less than 100 participants<sup>5-8</sup> treated with brachytherapy and even fewer treated with endoresection with the largest series of 41 participants undergoing primary endoresection<sup>7, 9-12</sup>. The small numbers in these series and the non-randomised nature of the studies make it difficult to draw conclusions about different treatment options. Shields and Shields et al<sup>13</sup> published visual outcomes of a large series of 1106 consecutive cases of plaque therapy patients and explored the risk factors for poorer outcomes using Cox proportional hazards regression models. The larger number in this series increases the precision of estimates. Meta-analyses<sup>14, 15</sup> have combined studies to increase sample size and study power.

The Collaborative Ocular Melanoma Study (COMS)<sup>16-18</sup> was a randomised trial involving 43 centres across the United States and Canada and recruited participants from 1986 to 1998. Six resource centres had roles in quality assurance of the study. 1317 participants were enrolled in the medium tumour trial and participants were followed for up to 15 years. This study was designed to overcome the challenges of studying an uncommon condition and enough participants could be recruited because of the large number of centres involved. One aim of the study was to

determine whether conservative (i.e. eye preserving) treatment with brachytherapy for medium sized tumours reduced survival compared to enucleation (eye removal). The outcome of the brachytherapy arm of this study is useful for comparison with other studies, including ours.

### **Treatment options for choroidal melanoma**

A variety of treatment options are available for the management of choroidal melanoma. More radical treatment involves removal of the eye (enucleation) which was the treatment of choice until more modern techniques became available. Enucleation is still necessary when a lesion is too large to treat, has caused extensive damage, or if other forms of treatment are unsuccessful.

Modern forms of treatment aim to conserve the eye. These include plaque brachytherapy (Ruthenium-106, Iodine-125 and Strontium-90), proton beam irradiation and trans-pupillary thermotherapy (TTT). Ruthenium-106 emits electrons and is used to treat tumours up to 5mm in thickness. It has a long half life of 368 days making it possible to use the same plaques for many patients. Iodine-125 emits gamma radiation and is able to treat thicker tumours (up to 10mm). Its half life is about 60 days. While Ruthenium-106 plaques come in premade sizes, Iodine-125 plaques are custom made for the individual tumour.

Surgical excision is possible and can be performed trans-scleral (from the outside of the eye)<sup>19</sup> or trans-vitreous (from the inside of the eye)<sup>9, 12, 20</sup>. Trans-vitreous excision is termed 'endoresection'. Combinations of these treatment methods are also used,

for example plaque radiotherapy combined with TTT or endoresection combined with plaque radiotherapy or TTT.

One aim of the COMS was to determine whether conservative treatment increased the risk of metastases and death compared with enucleation. The Medium Tumour Trial component of this study showed that all cause mortality rates following Iodine-125 brachytherapy did not differ from mortality rates following enucleation for up to 12 years after treatment <sup>21</sup>.

### **Brachytherapy outcomes**

#### *1) Visual loss*

Visual loss following brachytherapy is common during the first five years after treatment <sup>22</sup>. In the COMS, regardless of baseline visual acuity, the five year cumulative rate for visual acuity of LogMAR 1.00 or worse was 63% (CI, 59%-68%); for visual acuity of LogMAR 1.60 or worse, the rate was 45% (CI,41%-50%). Sia and Harper et al<sup>6</sup> found no correlation between visual outcome and tumour size or location but others suggest that retention of vision may be more likely if the tumour is more than 3 mm from the optic disc and fovea and if the vision is good at presentation <sup>7</sup>.

In a review of 1300 consecutive patients treated with brachytherapy <sup>13</sup>, 1106 had visual acuity of LogMAR 0.70 or better at the time of treatment. In this group poor visual acuity (LogMAR 1.00 or greater) was found in 34% at 5 years and 68% at 10 years of follow-up. When analysing visual outcome with regard to tumour thickness,

ultimate poor visual acuity of LogMAR 1.00 or worse was found in 24% with small tumours (<3.0mm thick), 30% with medium tumours (3.1-8.0mm), and 64% with larger tumours (>8.0mm). Tumours less than 5 mm from the optic disc or fovea demonstrated poor visual acuity in 35% at 5 years, whereas those 5mm or more from the optic disc and fovea showed poor visual acuity in 25% at 5 years. Van Ginderdeuren and Van Limbergen et al<sup>23</sup> suggest that Strontium-90 treatment may result in better visual outcomes. The most common causes of visual loss following brachytherapy are radiation maculopathy and cataract.<sup>35</sup> By 5 years after brachytherapy 83% of COMS participants had developed cataract. The most common cause of failure of vision to improve after cataract surgery was the presence of radiation maculopathy.

Management of radiation maculopathy has included laser photocoagulation, photodynamic therapy, intravitreal steroids and, more recently, intravitreal anti-vascular endothelial growth factor (anti-VEGF) treatments. Stability or improvement of visual acuity may be achieved in approximately 50% of cases. Central macular thickness has been shown to improve although the effects may only be short-lived and the benefits in those with longstanding macular oedema are less clear.<sup>36</sup>

In addition, plaque designs are being improved to provide a more 'collimated' radiation to reduce collateral retinal injury.<sup>36</sup>

## *2) Tumour recurrence / local control*

In the COMS the treatment failure rate (tumour growth, recurrence or extra-scleral extension) was 10.3% (CI, 8.0%-13.2%) at 5 years<sup>24</sup>. Treatment was more likely to fail with increasing patient age, increase in tumour thickness and more posterior location. Similarly, an 8% failure rate at 5 years was found in a study with Strontium-90<sup>23</sup>. Other studies by Sia and Harper et al<sup>6</sup> and Krohn and Monge et al<sup>8</sup> with up to 3 years follow-up have found local failure between 3.6% and 14.3%

### *3) Globe retention (enucleation)*

Enucleation rates vary across studies. In a study of 49 eyes by Sia and Harper et al<sup>6</sup> the all cause enucleation rate was 24.5% over 39.5 months. In contrast, by five years 12.5% (CI, 10.0%-15.6%) of the COMS patients required enucleation<sup>24</sup>. Failure to control the growth of the lesion was a more common cause of early enucleation whereas pain was more likely to cause patients to undergo enucleation beyond three years. The COMS found that risk for enucleation was increased with increasing thickness of the lesion, a more posterior location of the posterior tumour edge and poor presenting visual acuity.

Other studies suggest that between 5% and 10% of patients treated with brachytherapy ultimately require enucleation<sup>24-26</sup>. Retention of the eye may be more likely if the tumour is less than 16mm in diameter, less than 6mm thick and more than 3mm from the disc and fovea<sup>7</sup>.

### *4) Metastases / Survival*

Metastatic spread of ocular melanoma is haematogenous and the most common organ involved is the liver. Once systemic spread occurs, prognosis is normally poor with the median time from diagnosis of metastases to death of less than 6 months<sup>27</sup>.

The five year metastasis rate for histologically confirmed melanoma was 10% in the plaque treatment arm of the COMS Medium Tumour Trial<sup>17</sup>. The adjusted estimate for 5 year survival was 82%<sup>14, 21</sup>.

A meta-analysis of 1066 patients treated with Ruthenium plaque therapy found a 5-year melanoma related mortality of 6% for small / medium tumours and 26% for large tumours<sup>14</sup>.

Five year survival following brachytherapy appears to lie between 80 and 90%<sup>6, 23</sup> although smaller series have found higher 5 year mortality<sup>28</sup>. A recent systematic review<sup>2</sup> of 4070 patients with primary uveal melanoma found an 81.6% five year survival which is similar to the range of 77% to 84% reported by Singh and Topham<sup>15</sup> who reviewed survival over the 25 years 1973 to 1997.

Patient age and tumour size may best predict death from all causes and from metastases<sup>21</sup> and the rate of metastases increases with size of the tumour at presentation<sup>27</sup>. Largest tumour diameter is currently the most widely used predictor of metastatic death<sup>17, 28</sup>. Prediction of metastasis can be improved if genetic and histological tumour characteristics are also considered. According to Damato and Coupland<sup>31</sup> histological and genetic features add significantly in determining

prognosis. A recent analysis of 220 choroidal and ciliary body melanomas revealed that monosomy 3 (Hazard Ratio 2.83) and gain of chromosome 8 (HR 3.13) are important prognostic factors. High percentage of monosomy 3 and gain on chromosome 8 strongly correlated with poor survival.<sup>37</sup> The implication of this is that tissue samples from biopsies will play an increasingly important role. In addition, the detection of circulating malignant cells in the blood may play a future role in the diagnosis and management of metastatic disease<sup>30</sup>.

The theory that some patients have 'non-lethal' tumours based on genetics and histology makes the generalised results of the COMS study less definitive and a more individualised approach to prognosis is needed.

### **Endoresection**

High doses of radiation required to treat larger tumours result in significant ocular morbidity. This can be avoided if the tumour is initially resected, thus reducing the dose of radiation used as consolidation treatment. Tumours growing into the visual axis but which do not directly involve the foveal and optic disc areas are particularly good candidates for resection with the aim being to clear the visual axis and improve vision. García-Arumí and Sararols et al<sup>10</sup> treated 25 eyes with high (>9mm thick) posterior choroidal melanoma with promising results although follow-up was short (median 31 months). Although tumours involving the ciliary body may be amenable to trans-scleral resection, endoresection is generally not performed on these more anterior tumours. Other reasons for excluding tumours for endoresection include

basal diameter exceeding 10mm or if more than one third of the optic disc margin is involved<sup>9</sup>.

An additional advantage of the procedure is the availability of tumour material. Histological factors such as epithelioid cell type, closed loop patterns and high mitotic rate, and cytogenetic factors such as chromosome 3 deletions and gains on chromosome 8 correlate with largest tumour diameter which in turn correlates with metastatic death<sup>31, 37</sup>.

### **Endoresection outcomes**

#### *1) Visual loss*

Visual outcomes vary depending on the location of the tumour and are affected by complications of treatment. Retinal detachment is a significant complication occurring in 9.4% to 32.6% of cases and the development of cataracts attributed to silicone oil from 25% to 48%<sup>9, 10, 20</sup>.

García-Arumí and Sararols et al<sup>10</sup> achieved a mean of 20/100 (LogMAR 0.7) (range from LogMAR 3.0 to LogMAR 0.18) in 25 eyes after 31 months and, in another series<sup>12</sup>, 15% achieved better than 20/200 over 70.6 months. In the series by Karkhaneh and Chams et al<sup>20</sup>, only 13% of 15 non-enucleated eyes were better than CF over 89 months although the tumours involved the fovea in 45% of cases. Kertes and Johnson<sup>32</sup> achieved 6/60 or better in 31.2%. In Damato and Groenewald's early series<sup>9</sup> of 36 non-enucleated eyes 50% were CF to 6/60 and 14% better than 6/60 over a median of 20 months.

## *2) Tumour recurrence / local control*

Local tumour recurrence rates after endoresection vary. Seven (17%) of 41 patients undergoing endoresection with laser consolidation to the tumour bed had subsequent laser at the margin of the resection because of increased pigmentation although definite recurrence was not diagnosed<sup>9</sup>. Damato suggests a 10% local recurrence after endoresection<sup>26</sup>. Local recurrence was documented in 5.8% by García-Arumí and Zapata et al<sup>12</sup>.

## *3) Globe retention (enucleation)*

In Karkhaneh and Chams series<sup>11</sup> of 20 eyes, two eyes (10%) were enucleated intraoperatively due to severe haemorrhage and a further three eyes (15%) were enucleated over a mean follow-up of 89 months for recurrence (2 eyes) and development of a painful blind eye (1 eye). Seventy five percent of eyes were retained. Others have achieved higher retention rates of 90% over median of 20 months<sup>9</sup>, 92.1% of 38 eyes over 70.6 months<sup>12</sup> and 100% of 25 eyes over 31 months<sup>10</sup>. Reasons for enucleation included blind, painful eyes, severe intraocular haemorrhage, tumour recurrence, patient preference, intractable retinal detachment, phthisis bulbi and endophthalmitis.

### *Consolidation treatment*

Consolidative treatment may be applied to the tumour bed following resection. Options include plaque therapy or photocoagulation. In Damato and Groenewald's earlier series<sup>9</sup>, they treated the entire bed of the surgical coloboma and the margins of the choroid with strong laser burns in an attempt to destroy any residual tumour cells. In addition, cryotherapy was applied to the sclerotomies to destroy any tumour cells that may have seeded to these areas. In this series and others<sup>10</sup>, if tumour removal was uncertain a Ruthenium-106 plaque was applied to the sclera to irradiate the tumour bed, care being taken to reduce optic nerve radiation. In the same author's hands it became routine practice to perform adjunctive plaque radiotherapy after local resection after 1995<sup>33</sup> and in other centres since 2003<sup>12</sup>. If endoresection is performed in our department, it is standard treatment to consolidate with an Iodine-125 plaque

Authors of a more recently published study<sup>11</sup> highlight the option of endoresection in regions of the world where radiotherapy may not be available. In the absence of radiation services their surgical excision was consolidated with laser photocoagulation to the scleral bed at the time of excision. . As most of the endoresections in this study were performed by specialists outside our centre the routine use of Iodine-125 consolidation is inconsistent. It is also important to note that the doses of consolidation treatment with radiation (when used) are significantly lower than plaque brachytherapy alone. Endoresection should therefore not simply be considered an adjunct to brachytherapy.

#### *4) Metastases / survival*

The same authors<sup>11</sup> found a 5% mortality due to metastases at 7.5 years and local recurrence at the margin of the surgical coloboma in one of 20 patients (5%) over a similar time period.

With endoresection techniques, Kertes and Johnson et al<sup>32</sup> consolidated with tumour bed photocoagulation and found 9.4% (three of 32 patients) mortality due to distant metastases at 3.5 years. Damato and Groenewald et al<sup>9</sup> found 2% mortality from metastases over 41 month follow up. In this series selected patients received Ruthenium-106 plaque consolidation when the tumour margins were indistinct. García-Arumí and Sararols et al<sup>10</sup> also routinely applied photocoagulation to the scleral bed unless there were tumour remnants which could not be resected. They then applied a Ruthenium-106 applicator. They showed no mortality due to metastases after 2.5 years follow up. In a further study<sup>12</sup> the same authors failed to demonstrate statistical difference in survival with the use of post-operative brachytherapy although the comparison may not have been reliable due to study design. A review from 2004 suggested that there is no current evidence that local resection of posterior uveal melanoma is any different from enucleation or radiation with regard to patient survival<sup>34</sup>.

## Summary and interpretation of literature (not all studies are included)

Table 2 summarises some of the important study findings:

**Table 2: Summary of study outcomes**

Outcome	Brachytherapy			Endoresection		
	Outcome	Time	Author	Outcome	Time	Author
Visual acuity	63%>LogMAR 1.00	5 years	(22)	Mean LogMAR 0.70	31 mo	(10)
	34%>LogMAR 1.00	5 years	(13)	13%>LogMAR 2.00	89 mo	(11)*
	35%>LogMAR 1.00	5 years	(23)	64%>LogMAR 2.00	20 mo	(9)
Recurrence	10.3%	5 years	(24)	10%		(26)
	8%	5 years	(23)	5.8%		(12)
	3.6-14.3%	3 years	(6,8)			
Enucleation	12%	5 years	(24)	25%	89 mo	(11)
	24.5%	39.5 mo	(6)	10%	20 mo	(9)
	5-10%		(24-26)	0%	31 mo	(10)
				7.9%	70.6 mo	(12)
Survival	All cause			Metastases specific		
	82%	5 years	(14,21)	92.5%	5 years	(20)
	80-90%	5 years	(6,23)	90.6%	3.5 years	(32)
	81.6%	5 years	(2)	98%	41 mo	(9)
			100%	2.5 years	(10)	

\*45% of cases involved the macula

## Conclusion

There is heterogeneity in the reporting of visual outcomes and variation in follow-up time which makes meaningful comparison difficult. In addition the all-cause mortality reported in most brachytherapy studies is not comparable to the metastases specific mortality rates reported in the endoresection studies.

The above outcomes are based on case series and meta-analyses for the two treatments independently. There is a lack of comparative data of different treatment methods in the management of choroidal melanoma. There are significant barriers to the likelihood of randomised trials being performed, particularly regarding brachytherapy and endoresection. This is because there is higher risk of significant

ocular and potentially systemic complications related to endoresection and the associated ethical considerations around treatment decisions. There may, however, be advantages to performing endoresections in certain patients particularly with regard to visual outcomes. Our study compares brachytherapy and endoresection and seeks to address this issue.

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# Brachytherapy and Endoresection in the Treatment of Choroidal Melanoma in South Africa. (For submission to: RETINA®)

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The authors have no proprietary interest in any aspect of this study.

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**Index words****Key words**

Brachytherapy

Choroidal melanoma

Endoresection

Uveal melanoma

**Summary statement**

Selection of patients for endoresection based on tumour characteristics may result in better visual outcomes. We found no difference in recurrence rates, enucleation rates and metastases or death between these treatment methods.

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## **Purpose**

To report and compare the outcomes of brachytherapy and endoresection in the treatment of medium sized choroidal melanoma in South Africa.

## **Methods**

Retrospective cohort study. Consecutive participants undergoing brachytherapy for medium sized choroidal melanoma were compared with a cohort of participants undergoing endoresection. Primary outcomes were final best corrected visual acuity, recurrence rates, enucleation rates and rates of metastases or death. Regression models were used to examine patient and tumour characteristics for predictors of outcomes.

## **Results**

One hundred and sixty two brachytherapy and 25 endoresection participants were followed for a median of 56.4 and 56.3 months respectively. Tumours undergoing endoresection were thicker (6.6mm vs. 4.6mm,  $p<0.001$ ) and further from the fovea (5.1mm vs. 3.8mm,  $p=0.04$ ). Forty percent in each group maintained a visual acuity of 6/18 or better. The odds of poor visual outcome were 4.2 times higher in the brachytherapy group ( $p=0.046$ ). Presenting visual acuity, tumour thickness and distance from the fovea were associated with poor visual outcomes. Recurrence rates, enucleation rates and metastases or death were similar in each group. Recurrence was more likely with lesions closer to the optic disc. Risk of enucleation increased with tumour thickness ( $p=0.033$ ). Tumour thickness may be associated with increased risk of metastases or death ( $p=0.09$ ).

## **Conclusion**

Endoresection may offer patients with medium sized choroidal melanoma better visual outcomes if tumours are tall and more than 5mm from the fovea.

## Introduction

Conservative management of choroidal melanoma aims to effectively treat the tumour, preserve the globe, and retain visual function if possible. Brachytherapy<sup>1-3</sup>, charged particle irradiation<sup>4</sup> and surgical excision<sup>5-8</sup> are all well described. Plaque brachytherapy is the most commonly used treatment and is supported by the results of the Collaborative Ocular Melanoma study (COMS) which showed no increase in mortality comparing brachytherapy with enucleation<sup>9</sup>. Endoresection was described in 1986<sup>10</sup> and a number of series have been published<sup>5-7, 11</sup>.

The main causes of visual loss among brachytherapy patients are cataract and radiation maculopathy. Patients undergoing endoresection often undergo lens extraction at the time of surgery but may suffer severe intraoperative haemorrhage or postoperative retinal detachment. Adjunctive radiotherapy used in these patients is of lower dose as only the tumour base is treated which may help to limit radiation related visual loss. Although visual loss is common with both treatment methods, there is no current evidence that brachytherapy has favourable outcomes compared to endoresection and no randomised trials have been performed.

Patients are treated by both techniques in South Africa. Groote Schuur Hospital is the only centre to provide brachytherapy for the treatment of uveal melanoma. Patients are referred from private and public facilities throughout the country as well as from neighbouring countries. A database has been in place since Iodine-125 brachytherapy was pioneered in the 1970's but few results have been published<sup>12</sup>. Endoresection is performed in a number of centres nationally but little is known about the outcomes of this procedure in this setting.

In this study we examine and compare the outcomes of patients undergoing brachytherapy for choroidal melanoma at Groote Schuur Hospital and patients undergoing endoresection from a national database.

### **Patients and Methods**

We conducted a retrospective cohort study comparing two groups of participants, one undergoing brachytherapy and the other endoresection for the treatment of medium sized choroidal melanoma. The brachytherapy group was sourced from the database of choroidal melanoma patients collected by the department of Radiation Oncology at Groote Schuur Hospital. Exclusion criteria included tumours that extend into the ciliary body, tumours more than 10mm in height and / or 16mm in widest basal diameter and patients with less than 6 months follow-up. Treated patients were followed up by their referring ophthalmologists. Follow-up data were obtained from these ophthalmologists from whom six monthly clinical updates were routinely requested.

Endoresections are performed by a small group of vitreo-retinal surgeons in the country. Specific email notification was sent to five surgeons with known experience in this procedure informing them of the proposed data collection and requesting their contribution to the database. Four of the five responded (see appendix B) and submitted information on all endoresections they had performed. All data were entered into a standardised database designed for the study which had been sent to each participating surgeon. In addition, all other members of the South African Vitreo-Retinal Society (SAVRS) were contacted via the society email list or telephone inviting participation in the study. No other retinal surgeons had experience with endoresections. Analysis was restricted to those patients receiving endoresection as the primary treatment of the melanoma. Tumour characteristics and follow-up criteria were similar to those in the brachytherapy group.

Baseline observations included date of birth, gender, date of diagnosis, left or right eye, pre-operative visual acuity, presence of other non-associated pathology and type and date of the procedure performed. The documented preoperative tumour characteristics were height (thickness), largest basal diameter, distance from the optic disc and fovea, location within the eye (predominant quadrant), and the presence or absence of an associated exudative retinal detachment.

Follow-up data included final best corrected visual acuity and any complications related to the tumour or treatment. Tumour recurrence, enucleation of the globe, presence of metastases and death from all causes were outcomes of interest. Snellen acuity and decimal acuity were converted to the logarithm of the minimal angle of resolution (LogMAR acuity) for analysis. Light perception and no light perception outcomes were not included in the calculation of mean visual acuity but were assigned a LogMAR of 5.0 for categorical analysis<sup>13</sup>. Recurrence of tumour growth was made on the basis of clinical examination and ultrasound measurements or confirmed on histology in enucleated eyes. Diagnosis of metastases was usually made on ultrasound of the liver and confirmed by an oncologist.

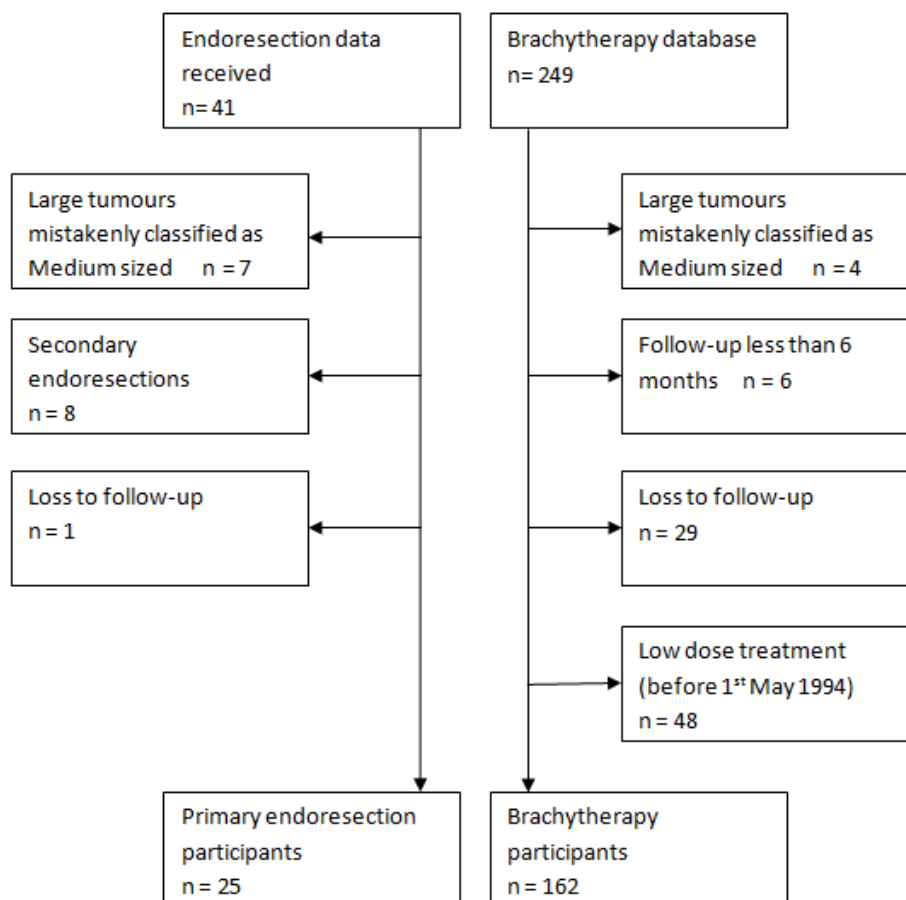
Statistical analysis was done using STATA 11.0 (StataCorp. LP, USA). A logistic regression model was used to estimate prognostic factors for poor visual outcome. The Kaplan-Meier method was used to analyse survival proportion until recurrence, enucleation and metastases or death from all causes. Cox regression analysis was used to estimate prognostic factors for these outcomes.

## Results

### 1) Participants excluded from analysis

Participants were excluded from the analysis for the following reasons: Seven of the 41 patients in the endoresection group and four of the 249 in the brachytherapy group had large tumour characteristics despite being classified as medium size. Eight endoresections had been performed as secondary treatment. Follow-up information was not available for one patient in the endoresection group and 29 patients in the brachytherapy group. At least six months follow-up data were available on 25 patients undergoing primary endoresection and 210 patients undergoing brachytherapy. It was discovered that prior to 1<sup>st</sup> May 1994, while brachytherapy was still being developed, a sub therapeutic dose was being administered. The 48 participants treated prior to that date were therefore excluded from the analysis (see Figure 1). (These participants are analysed in Appendix G).

**Figure 1: Participants**



## 2) Baseline characteristics

The mean age at diagnosis, gender, laterality (left or right eye), presence of exudative retinal detachment and baseline visual acuity were similar in each group. The baseline characteristics of each group are summarised in Table 1. The tumours undergoing endoresection were significantly thicker than those receiving brachytherapy (mean of 6.6mm vs. 4.6mm.  $P < 0.001$ ) and the mean distance from the fovea was greater in the endoresection group (5.1mm vs. 3.8mm.  $p=0.04$ ). About 70% of patients in both groups had 6/18 or better Snellen acuity at the time of diagnosis.

**Table 1: Baseline characteristics**

<b>Variable</b>	<b>Endoresection (n=25)</b>	<b>Brachytherapy (n=162)</b>	<b>p-value</b>
<b>Age at diagnosis (median)</b>	56.5	59.1	0.27
<b>Gender</b>	15 Male 10 Female	73 Male 89 Female	0.16
<b>Laterality</b>	13 Right 12 Left	83 Right 79 Left	0.94
<b>Presenting Visual Acuity (mean)</b>	LogMAR 0.66 Snellen 6/27	LogMAR 0.60 Snellen 6/24	0.68
<b>Category at diagnosis (%)</b>			
<b>1</b> Snellen 6/5 to 6/18 LogMAR -0.08 to 0.48	19 (76.0)	111 (68.5)	0.43
<b>2</b> Snellen 6/24 to 6/48 LogMAR 0.60 to 0.90	0 (0.0)	12 (7.4)	
<b>3</b> Snellen 6/60 to 3/60 logMAR 1.00 to 1.30	1 (4.0)	16 (9.9)	
<b>4</b> 2/60 or worse LogMAR 1.48 or worse	5 (20)	23 (14.2)	
<b>Tumour characteristics</b>			
<b>Height (mean)</b>	6.6mm	4.6mm	< 0.001
<b>Maximum basal diameter (mean)</b>	11.0mm	10.0mm	0.07
<b>Temporal or posterior pole</b>	15/25 (60%)	92/162 (56.8%)	0.76
<b>Distance to disc (mean)</b>	4.2mm	4.6mm	0.79
<b>Distance to fovea (mean)</b>	5.1mm	3.8mm	0.04
<b>Exudative Retinal Detachment</b>	12/21 (57.1%)	62/161 (38.5)	0.16
<b>Follow-up (median months)</b>	56.3	56.4	0.78
<b>Follow-up Range</b>	7.9 to 121.8	6.5 to 175.8	

The median follow-up was almost identical at 56.3 months in the endoresection group and 56.4 months in the brachytherapy group ( $p=0.78$ ).

### 3) Final visual acuity

Final visual acuity was available in 156 brachytherapy patients and all 25 endoresection patients. About 40% of both groups retained vision of 6/18 or better at the end of follow-up. Nine out of 25 (36%) endoresection and 70 out of 156 (45%) brachytherapy patients had 2/60 or worse at the last visit. We found that the odds of a poor visual outcome (visual acuity less than 2/60) was 4.2 times higher in the brachytherapy group compared to the endoresection group ( $p=0.046$ ) when controlled for presenting visual acuity and tumour characteristics. The outcomes are summarised in Table 2.

**Table 2: Outcomes**

<b>Visual outcome</b>	<b>Endoresection (n=25)</b>	<b>Brachytherapy (n=156)</b>	<b>P - value</b>
<b>Final visual acuity (mean)</b>	0.87	1.03	0.76
	Snellen +- 6/48	Snellen+- 6/60	
<b>1</b>	10 (40%)	60 (38.7%)	
<b>Snellen 6/5 to 6/18</b>			
<b>LogMAR -0.08 to 0.48</b>			
<b>2</b>	5 (20%)	16 (10.3%)	
<b>Snellen 6/24 to 6/48</b>			
<b>LogMAR 0.60 to 0.90</b>			
<b>3</b>	1 (4%)	9 (5.8%)	0.52
<b>Snellen 6/60 to 3/60</b>			
<b>logMAR 1.00 to 1.30</b>			
<b>4</b>	9 (36%)	70 (45.2%)	
<b>2/60 or worse</b>			
<b>LogMAR 1.48 or worse</b>			
<b>Other outcomes</b>	<b>Endoresection (n=25)</b>	<b>Brachytherapy (n=162)</b>	<b>P - value</b>
<b>Recurrence</b>	5 (20%)	23 (14.2%)	0.54
<b>Enucleation</b>	2 (8%)	16 (9.9%)	1.00
<b>Metastases or death</b>	5 (20%)	21 (13.0%)	0.35

Of the non-enucleated eyes that retained better than PL vision (21 in the endoresection group and 124 in the brachytherapy group), the mean visual acuity was logMAR 0.87

(Snellen acuity 6/48) in the endoresection group and LogMAR 1.03 (Snellen acuity 6/60) in the brachytherapy group ( $p=0.76$ ).

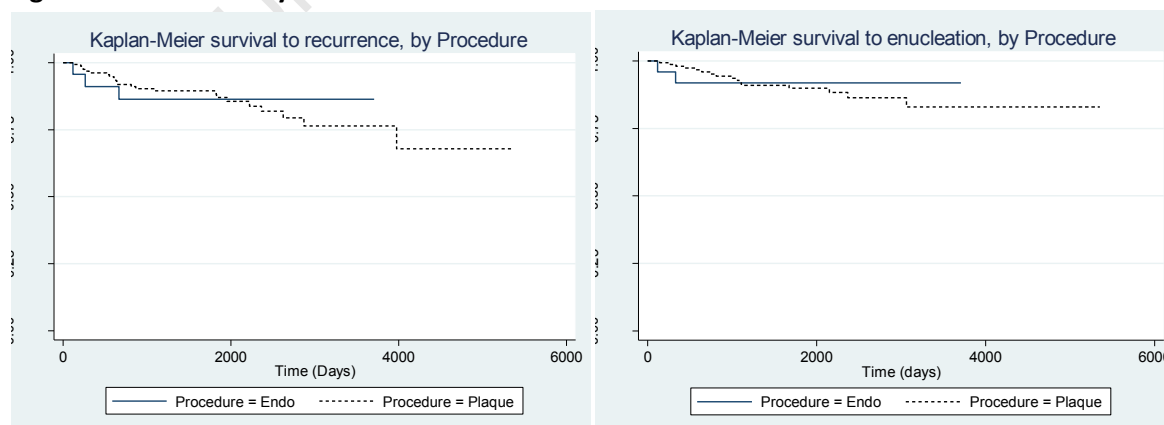
Poor visual outcome (2/60 or worse) was associated with poorer visual acuity at presentation, increase in tumour height and smaller distance to the fovea. Participants presenting with visual acuity of 6/60 were 1.9 times more likely to experience poor outcome than those presenting with normal vision ( $p=0.03$ ). Each 1mm increase in height was associated with 43% increase odds of poor visual outcome ( $p=0.006$ ) and each millimetre further from the fovea was associated with 32% reduction in odds of a poor visual outcome ( $p=0.006$ ). (The final logistic regression model can be seen in Appendix H.)

#### 4) Rates of recurrence, enucleation, metastases or death

We found no difference in the rates of recurrence (20% vs. 14.2%, ( $p=0.55$ ), enucleation (8% vs. 9.9%,  $p=1.00$ ) or metastases / death (20% vs. 13%,  $p=0.35$ ) between the endoresection and brachytherapy groups respectively (see Table 2).

Survival times to recurrence, enucleation and metastases or death are shown in Figure 2.

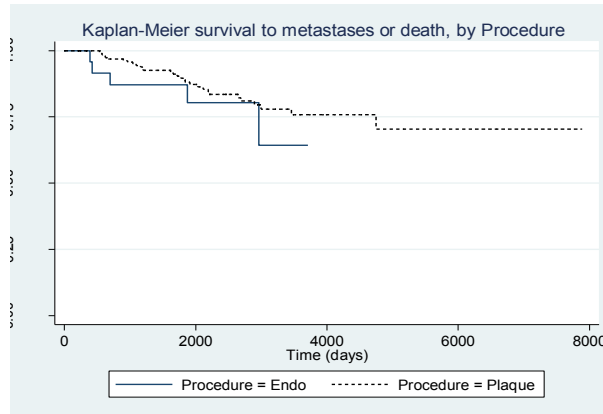
**Figure 2. Survival analysis**



Tumour recurrence survival curves ( $p=0.89$ )

Enucleation survival curves ( $p=0.72$ )

**Figure 2. Survival analysis (continued)**



Metastases or death survival curves ( $p=0.32$ )

Seventy five percent of the brachytherapy group had no recurrence by 130.6 months and 75% of the endoresection and brachytherapy groups had no metastases or death until 97 and 156 months respectively. There was no difference in survival curve estimates of time to recurrence ( $p=0.89$ ), time to enucleation ( $p=0.72$ ) or time to metastases or death from any cause ( $p=0.32$ ) between the treatment groups.

Cox regression modelling (See Appendix H) revealed that for each millimetre further from the optic disc the hazard of recurrence was reduced by 31% ( $p=0.016$ ). Age at diagnosis, lesion height and widest diameter were not associated with risk of recurrence. Increase in tumour thickness was associated with increased risk of enucleation ( $p=0.033$ ). Each year of increased age at presentation was associated with an 8.6% increased risk of metastases or death from any cause during the follow-up period ( $p<0.001$ ). Our data suggest that tumour height may be associated with increased risk of metastases or death ( $p=0.09$ ).

## Discussion

While a number of globe sparing treatments are available in the management of choroidal melanoma there are no randomised trials comparing brachytherapy and endoresection. Because of the low incidence of choroidal melanoma, the individuality of tumour characteristics and higher risk of complications associated with endoresections it is unlikely that such studies will be undertaken. We have compared two cohorts of patients undergoing these procedures in an attempt to identify potential benefits.

We found good visual outcomes (LogMAR < 0.48) in a similar proportion (40%) of each group. However, the odds of poor visual outcome (LogMAR > 1.48) was 4.2 times greater in the brachytherapy group (p=0.046). Our study agrees with other larger series that good presenting vision, tumour thickness and greater distances from vital structures (optic disc and fovea) are correlated with visual outcomes<sup>2,14</sup>.

Loss of vision is a common and expected complication of both brachytherapy and endoresection. Forty five percent of the COMS patients had visual acuity of LogMAR 1.60 or worse at 5 years<sup>1</sup>. We found a similar outcome (LogMAR >1.48 in 45.2% at a mean of 59 months) among brachytherapy patients although our data represent a mean visual acuity with outcomes from 6 months to nearly 15 years. Visual results following endoresection vary with few series achieving good outcomes. Vision better than 6/60 (LogMAR 1.00) has been achieved in 14% - 31%<sup>5,7,15</sup>. One series of 25 eyes<sup>6</sup> performed on particularly tall tumours, none of which involved the macula, achieved a mean of 6/30 (LogMAR 0.7) after 31 months. In our study the mean tumour thickness was significantly higher (6.6mm vs. 4.6mm) and the tumour base significantly further (5.1mm vs. 3.8mm) from the fovea at baseline in the endoresection group. This selection of patients into the endoresection group may explain better visual results than other series and supports the findings of García-Arumí and Sararols et al<sup>6</sup> that this group of patients may achieve better visual results with endoresection.

Treating tall tumours with radiation delivers a high global dose to achieve therapeutic levels at the tumour apex. This increases the risk of poor visual outcomes. In these instances it is advantageous to remove the bulk of the tumour and apply a lower dose of radiation or laser to the tumour bed. Despite early recommendations<sup>5</sup> to resect tumours close to the optic disc, endoresection may be considered in those where the tumour base is further from vital posterior structures. Tall tumours invading the visual axis with a small base away from the posterior pole may therefore be the ideal cases to experience visual benefit of endoresection. As we only analysed final visual acuity we were unable to demonstrate trends of visual loss. One might expect a time related loss of vision among brachytherapy patients due to cataract formation and radiation maculopathy but a more dramatic initial reduction in endoresection patients (as a result of surgery) followed by stabilisation.

Tumour recurrence following brachytherapy varies between 3.6% and 14.3%<sup>3, 16, 17</sup>. The COMS showed a recurrence rate of 10.3% (CI 8.0% – 13.2%) at 5 years<sup>18</sup>. We found a recurrence rate of 14.2% at a median follow up of 59.1 months. Rates of recurrence following endoresection vary from 5.8%<sup>7</sup> and up to 10%<sup>19</sup>. Five out of 25 (20%) of our patients experienced clinical recurrence which was higher than other reports. The likelihood of recurrence following endoresection may be significantly influenced by the concurrent use of brachytherapy or laser therapy to the sclera bed following resection. In our study only three patients received plaque brachytherapy alone following endoresection. Twenty received laser alone and one patient received laser and brachytherapy. Four of the 5 recurrences following endoresection had not received concurrent brachytherapy. Three of these recurred despite laser to the tumour bed. Others have found recurrence of 3% to 5% following laser consolidation alone<sup>11, 15</sup>. It has become increasingly common to consolidate the tumour bed with brachytherapy in many centres<sup>7, 20</sup> and this is now standard in our

hospital. Our study found that recurrence was more likely with lesions closer to the optic disc ( $p=0.016$ ) but was underpowered to demonstrate a statistical difference between recurrence rates in patients receiving endoresection (with or without consolidation) and brachytherapy.

Enucleation rates following brachytherapy vary between 5% and 25%<sup>16, 18, 19, 21</sup>. The COMS found a 12.5% enucleation rate at five years. Series of endoresected patients report globe retention of 75% over 89 months<sup>22</sup>, 92% over 70.6 months<sup>7</sup> and 100% over 31 months<sup>6</sup>. We found enucleation rates of 8% in the endoresection group and 10% in the brachytherapy group ( $p=1.00$ ). Similar to other studies<sup>14</sup> we found that risk of enucleation increased with tumour thickness ( $p=0.033$ ) but we did not find an association with tumour diameter and proximity to the disc or fovea.

Five year survival following brachytherapy is estimated at around 82%<sup>9, 23, 24</sup> and has remained similar over the past 35 years<sup>25</sup>. Small series of endoresections looked at metastases related mortality (not all cause) and found rates between 0% over two and a half years<sup>6</sup> and 9.4% over three and a half years<sup>15</sup>. We found an all cause mortality of 13% and 20% in the brachytherapy and endoresection groups respectively ( $p=0.35$ ). Our findings agree with others that age ( $p<0.001$ ) and possibly tumour thickness ( $p=0.09$ ) best predict death from all causes and metastases<sup>9</sup>. Largest tumour diameter is often used as a predictor of metastatic disease<sup>26, 27</sup> but we could not corroborate this finding. It is now thought that histological and genetic features of tumours are increasingly important in determining prognosis<sup>28</sup>. The implication of this is that increasing numbers of tumours are likely to undergo biopsy as part of their management and that prognosis will need to be individualised.

The study of rare conditions such as choroidal melanoma is difficult, particularly when randomised trials are unlikely to be performed. Our study attempts to compare two cohorts of patients but has limitations. 3.8% of the endoresection group and 15.2% of the brachytherapy group were lost to follow-up. While those who were lost were significantly older (65.3 vs 58.0 years,  $p=0.005$ ) this was not differential with respect to procedure performed and is unlikely to represent bias. Small numbers in the endoresection group significantly under power the statistical comparison of the groups. Selection of patients with thicker tumours further from the fovea into the endoresection group is present at baseline. The more favourable visual outcomes in the endoresection group may suggest that there is benefit in this procedure for patients with these tumour characteristics, and therefore provides an important finding.

Visual preservation where possible is an important consideration in the management of choroidal melanoma. We would recommend considering endoresection in patients with medium sized choroidal melanoma if tumours are tall and more than 5mm from the fovea. Further studies are needed in this area.

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08 September 2008

REC REF: 391/2008

Dr James Rice  
Ophthalmology

Dear Dr Rice

**PROTOCOL: ENDORESECTION FOR CHOROIDAL MELANOMA A REVIEW OF PATIENTS TREATED IN SOUTH AFRICA**

Thank you for submitting your study to the Research Ethics Committee for review.

It is a pleasure to inform you that the Ethics Committee has **formally approved** the above-mentioned study

**Approval is granted for one year till the 15<sup>th</sup> September 2009.**

Please submit an annual progress report if the research continues beyond the expiry date. Please submit a brief summary of findings if you complete the study within the approval period so that we can close our file.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

**Please quote the REC. REF in all your correspondence.**

Yours sincerely

**PROFESSOR M BLOCKMAN**  
**CHAIRPERSON, HSF HUMAN ETHICS**

Federal Wide Assurance Number: FWA00001637.  
Institutional Review Board (IRB) number: IRB00001938

lemjedi



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10 January 2011

HREC REF: 391/2008

Dr JC Rice  
Ophthalmology  
H53, OMB

Dear Dr Rice

**PROJECT TITLE: ENDORESECTION FOR CHOROIDAL MELANOMA A REVIEW OF PATIENTS TREATED IN SOUTH AFRICA**

Thank you for submitting your letter to the Faculty of Health Sciences Human Research Ethics Committee dated 21 December 2010.

Approval is granted for a further 12 months until 15 January 2012. This approval includes the amendment to add a second database in the analysis.

Please submit an annual progress report if the study continues beyond the approval period.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please quote the REC. REF in all your correspondence.

Yours sincerely

**PROFESSOR M BLOCKMAN**  
**CHAIRPERSON, HSF HUMAN ETHICS**

**Appendix B**  
**Invitation to participate**

Surgeons known to perform endoresection for choroidal melanoma in South Africa:

**Dr. Raoul Scholtz**

Melrose House  
14 Palmyra Road  
Claremont 7708  
Cape Town

**Dr. Louis Kruger**

22 Hocky Avenue  
Northcliff 2195  
Johannesburg

**Dr. Kelvin Rivett**

18 St. James Road  
Southernwood 5201  
East London

**Dr. Robert Nutt**

PO Box 72579  
Parkview 2122  
Johannesburg

**Letter of invitation to other members of the South African Vitreoretinal Society**

Dear members of the SAVRS

I am performing a study comparing brachytherapy and endoresection for choroidal melanoma and I am putting together a national database of endoresection data from all those who perform the procedure.

Hence I would like to extend an invitation to all colleagues who have performed endoresection at any time to participate in the study. I hope that we will publish the data in a paper as the Choroidal Melanoma Endoresection Study Group with full acknowledgment of all contributors.

I hope to minimise demands on your time by producing tables and making data collection as easy as possible.

Please would you let me know by return email to [james.rice@uct.ac.za](mailto:james.rice@uct.ac.za) if you are willing to participate I would be most grateful.

Kind regards  
James Rice  
Groote Schuur Hospital  
Cape Town

## **Appendix C**

### **Data collected on each participant**

Treating ophthalmologist

Patient number

Date of birth

Gender

Eye (left or right)

#### **Preoperative data**

Date of diagnosis

Confirm absence of systemic metastases on liver ultrasound, chest X ray, liver function tests

Reason not for primary brachytherapy / for selecting endoresection

Best corrected pre-operative visual acuity

Non-associated ocular pathology

Tumour characteristics

Prior treatment

Location (predominant quadrant)

Height (mm)

Widest diameter (mm)

Distance to disc (mm)

Distance to fovea (mm)

Surgery (endoresection or brachytherapy)

Date of surgery

Endoresection technique used

Intra-operative events

Consolidation treatment

Yes / No

Plaque or laser

Second procedures performed later

Late complications

Pathology

Cell type

Genetics (if available)

#### **Post-operative data**

Final BCVA

Date of last visit

Presence of local recurrence

Date diagnosed

Enucleation

Yes / No

Date of enucleation

Reason for enucleation

Presence of metastases

Date diagnosed

Date of death

Tumour related Yes / No

## Appendix D: Instructions to Authors for submission to Retina



**Scope:** RETINA®, The Journal of Retinal and Vitreous Diseases, publishes original and special articles concerning disorders of the retina and vitreous.

**Ethical/Legal Considerations.** A submitted manuscript must be an original contribution not previously published (except as an abstract or preliminary report), must not be under consideration for publication elsewhere, and if accepted, it must not be published elsewhere in similar form, in any language, without the consent of Lippincott Williams & Wilkins. Each person listed as an author is expected to have participated in the study to a significant extent. Although the editors and referees make every effort to ensure the validity of published manuscripts, the final responsibility rests with the authors, not with the Journal, its editors, or the publisher. **All manuscripts must be submitted on-line through the journal's Web site at [www.retinajournal.com](http://www.retinajournal.com).** See submission instructions under "On-line manuscript submission."

**FINANCIAL DISCLOSURE:** Each author warrants that he or she has no commercial associations (e.g., consultancies, stock ownership, equity interest, patent/licensing arrangements, etc.) that might pose a conflict of interest in connection with the submitted article, except as disclosed on a separate attachment. All funding sources supporting the Work and all institutional or corporate affiliations of the authors are acknowledged in a footnote in the Work.

**Patient anonymity and informed consent.** It is the author's responsibility to ensure that a patient's anonymity be carefully protected and to verify that any experimental investigation with human subjects reported in the manuscript was performed with informed consent and following all the guidelines for experimental investigation with human subjects required by the institution(s) with which all the authors are affiliated. Authors should mask patients' eyes and remove patients' names from figures unless they obtain written consent from the patients and submit written consent with the manuscript.

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### **Manuscript Submission**

**On-line manuscript submission:** All manuscripts must be submitted on-line through the Web site: [www.retinajournal.com](http://www.retinajournal.com). **First-time users:** Please click the Register button from the menu and enter the requested information. On successful registration, you will be sent an e-mail indicating your user name and password. Print a copy of this information for future reference. *Note:* If you have received an e-mail from us with an assigned user ID and password, or if you are a repeat user, do not register again. Just log in. Once you have an assigned ID and password, you do not have to re-register, even if your status changes (that is, author, reviewer, or editor).

**Authors:** Please click the log-in button from the menu at the top of the page and log into the system as an Author. Submit your manuscript according to the author instructions. You will be able to track the progress of your manuscript through the system. If you experience any problems, please contact us either by e-mail at [retina@retinajournal.com](mailto:retina@retinajournal.com) or 610-525-4849.

### **PREPARATION OF MANUSCRIPTS**

Manuscripts that do not adhere to the following instructions will be returned to the corresponding author for technical revision before undergoing peer review.

**Title Page.** Make the full title brief but meaningful. Make it explicit for indexing. The abbreviated title cannot be greater than 40 characters. List all authors by first name, middle initial, and last name, with highest academic or medical degree. When applicable, the footnote should include each author's departmental affiliation and the institution where the study was performed, grants and funds in support of the study, and if the paper was presented at a meeting, the name of the organization, place, and date on which it was read. The name and mailing address of the author to whom correspondence and requests for reprints should be directed must be provided. All manuscripts must have a sentence indicating whether any authors have a proprietary interest.

The title page must also include disclosure of funding received for this work from any of the following organizations: National Institutes of Health (NIH); Wellcome Trust; Howard Hughes Medical Institute (HHMI); and other(s).

**Key Words and Summary Statement.** On the second page, list words and terms in alphabetic order under which you believe the article should be indexed. The editorial board reserves the right to alter this list as it deems necessary. You may list up to 10 key words. Also include a brief summary statement (50 words or less) to be printed in the table of contents.

**Structured Abstract.** Page three of your manuscript must contain structured abstract of not more than 200 words. The abstract should be divided into four sections with the following headings: Background or Purpose, Methods, Results, and Conclusion.

**Text.** The introduction should be pertinent to the study but not an in-depth review of the literature. The materials, subjects, and methods should be clearly defined so that the study may be duplicated by other investigators. Results should be as concise as possible. The discussion is an explanation of the results of the study and should limit itself to the subject matter of the paper.

**Tables and figures are to be separate files that are submitted individually and cannot be embedded in the word document**

**Tables.** Double space each table in a separate file from that of the text. Number consecutively as they are presented in the text. A brief title for each table must be supplied. Give each column a short or abbreviated heading. Place explanatory matter in the footnotes, not in the heading. The following symbols are to be used in this sequence asterisk (\*), dagger (†), upside-down-dagger, double-dagger (‡), double asterisks (\*), 2 daggers, 2 upside-down-daggers, 2 double-daggers. Horizontal and vertical rules are to be omitted. Previously published data must be acknowledged fully and written permission for its use must be obtained. Each table should be self-explanatory, i.e., all information necessary to understand the table without the use of the text should be contained in the caption and the table itself. Due to space considerations, do not use a table for data that can be given in the text in one or two sentences.

**Figures.** Figures must be submitted as individual files. They cannot be embedded in the word document. Cite figures consecutively in the text, and number them in the order in which they are discussed. ♦ If the images are not of a high enough resolution to permit quality reproduction for publication purposes, they will be returned to the author.

Digital art should be created/scanned and saved and submitted as either a TIFF (tagged image file format), an EPS (encapsulated postscript) file. PPT (Power Point) files will also be accepted. **Electronic**

**photographs ♦ radiographs, CT scans, and so on ♦ and scanned images must have a resolution of at least 300 dpi. Line art must have a resolution of at least 1200 dpi (dots per inch).** If fonts are used in the artwork, they must be converted to paths or outlines or they must be embedded in the files. **Color images must be created/scanned and saved and submitted as CMYK files.**

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Supplemental Digital Content must be cited consecutively in the text of the submitted manuscript. Citations should include the type of material submitted (Audio, Figure, Table, etc.), be clearly labeled as "Supplemental Digital Content," include the sequential list number, and provide a description of the supplemental content. All descriptive text should be included in the call-out as it will not appear elsewhere in the article.

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All acceptable file types are permissible up to 10 MBs. For audio or video files greater than 10 MBs, authors should first query the journal office for approval. For a list of all available file types and detailed instructions, please visit <http://links.lww.com/A142>.

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In listed references, all names of authors should be given, unless there are more than four. If there are five or more, list the first three, followed by "et al." References to journal articles should include (1) author, (2) title, (3) journal name (as abbreviated in **Index Medicus**), (4) year, (5) volume number, and (6) inclusive page numbers, in that order. References to books should include (1) author(s), (2) chapter title (if any), (3) editor (if any), (4) title of book, (5) city of publication, (6) publisher, (7) year, and (8) page numbers. Volume and edition numbers, and names of translator should be included when appropriate.

The following style is used by the Journal for periodicals (1) and for books (2):

1. Jones IS, Jakobiec FA. Diseases of the Orbit. Hagerstown, MD: Harper & Row, 1979;9-17.

2. Smith BR. Diseases of the retina. Retina 1981; 1:25-28.

If there is any doubt about abbreviation of a journal name, it should be spelled out completely.

**Letters to the Editor:**

There are different types of Letters to the Editor (LTE). If the purposes of the LTE is to comment on a published article, the first sentence of the LTE should include the name of the published article's first author along with the title of the published article. The article discussed should then be referenced at this time or should be referenced at the end of the LTE. If the LTE is a reply to a previously submitted LTE, the first sentence should include the name of the letter's author and cite the letter as reference. The previously published article should then be referenced as well either in the body of the text or at the end of the response to the LTE. If the LTE is a reply/response which was solicited by the editors of RETINA, please submit the reply through the "Invited Commentary" process. Do not submit it as an original article or submission.

**Other Sections.** The journal also accepts manuscripts for other sections such as Review Articles, Diagnostic & Therapeutic Challenges, Correspondences (Letter to the Editor, and Response to Letter to the Editor), Clinicopathologic Correlations, Surgical Techniques, and New Instruments. All manuscripts must double-spaced, no more than 5 pages of manuscript text in length, and should include no more than 4 figures and 5 references. The format for all submitted manuscripts is basically as described above with a few exceptions. Review Articles are not limited in length. Diagnostic & Therapeutic Challenges require no abstract and have no limit for figures and references. Surgical Techniques and Clinicopathologic Correlations are treated like a full manuscript and require an abstract. All Correspondence and New Instruments should have a standard title page with full length title, running title, and author information. Key words and summary statement should be on the second page. A formal abstract is not required by the journal Retina for Correspondence and New Instruments. A summary statement of 50 words is necessary for publication and indexing and must be included at the time of submission. All pages must be numbered starting with the title page being page one. Each figure must be submitted separately. A figure with four parts (i.e. A, B, C, D) will be considered 4 figures. All color figures will be published in this section at the authors' expense. Authors who submit figures in color do so with the understanding that the figures will be published in color and at their expense.

Manuscripts submitted to Surgical Techniques must have an edited video of no longer than 3 minutes which demonstrates the salient aspects of the technique. The video should enhance, but not replace, the technique description in the manuscript. Please see the instructions on Supplemental Digital Content for the details concerning video submission.

The journal accepts manuscripts for consideration as photo essays. These essays include the visual presentation of material where the primary emphasis is on the images. These images can include color images, angiograms, optical coherence tomography, histologic sections, x-rays, ultrasounds, and other studies. The images can be an outstanding presentation of classic findings, atypical findings or new findings, but, the primary emphasis should be on the images. These are not case reports, but rather visual presentation of material as a teaching tool. The images need to be of the highest quality. The accompanying manuscript should be limited to a total of 300 words. A maximum of 5 separate images and 5 references can be included. All figures submitted in color are published in color, at the expense of the author. Please refer to the rest of the author instructions for other requirements for manuscripts submitted to Retina.

Each manuscript will be edited to conform with Editorial Board policy regarding spelling, punctuation, and typographic construction in accordance with "Uniform Requirements for Manuscripts Submitted to Biomedical Journals." As a guide, **The Manual of Style**, prepared by the Scientific Publications Division of the American Medical Association, may be used. When the manuscript has been set in type, proofs will be submitted to the author for approval. These must be returned with the original manuscript and illustrations as indicated on the proofs.

**Appendix E:**  
**Participant selection and data quality**

Choroidal melanoma is a condition that predominantly affects Caucasians. As many Caucasians in South Africa are of European descent it is likely that our results are comparable to other international study populations and not unique to an 'African' population. Given that Caucasians historically have had better access to medical care in South Africa it is likely that the participants undergoing endoresection and brachytherapy are representative of a similar source population.

The method of data collection and thus quality of data in each group was similar. Although baseline characteristics were collected and maintained in a central database in the brachytherapy group and collected from individual surgeons in the endoresection group there is no reason to believe that there should be a difference in baseline data quality. Similarly, all follow up data were collected in a similar method for both groups as all participants were followed up by suitably qualified ophthalmologists from around the country.

Most data are quantitative and specific and unlikely to be systematically different between the groups. Although early tumour recurrence is sometimes difficult to diagnose we have no reason to believe that there should be a difference in the clinical diagnosis of recurrence between the groups. We have already discussed the selection into the endoresection group of taller tumours further from vital structures within the eye. The reason for the difference in visual outcomes may be related to this selection bias highlighting the possible benefit of performing endoresections on these types of tumours.

Given the potential for more anaesthetic complications related to endoresection in older patients we might have expected selection of younger patients into the endoresection group but we found similar median ages in both groups.

Lack of randomisation to treatment arms, however, and certain tumour characteristics (e.g. tumour thickness) favouring selection for endoresection (selection bias) reduced the counterfactual comparison of the groups. There was also insufficient power to detect differences between treatment groups due to small numbers of endoresection patients.

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**Appendix F:**  
**Loss to follow up**

Loss to follow up data are summarised in the tables A and B below:

**Table A: Loss to follow-up by treatment group**

Loss to follow up	Endoresection	Brachytherapy	Total
<b>No</b>	25	162	187
<b>Yes</b>	1	29	30

P= 0.14 (Fisher's exact)

Loss to follow up of 30 participants (29 brachytherapy and 1 endoresection) reduced the precision of our estimates but was not significantly different between treatment groups (p=0.14). Baseline characteristics of the two groups are shown in Table B. Due to the small number of endoresections it is difficult to draw conclusions regarding the significantly older age of those lost to follow up (65.3 years vs. 58 years, p=0.005). Because the differential loss to follow up is only present with respect to this risk factor and not with respect to procedure this may not represent bias. Similarly the possible difference in widest diameter (10.5mm vs. 10.1mm, p=0.10) may not represent selection bias.

**Table B: Baseline characteristics**

Variable	Follow-up (n = 187)	Loss to follow-up (n=30)	p-value
<b>Age at diagnosis (mean)</b>	58.0	65.3	0.005
<b>Gender</b>	88 Male 99 Female	13 Male 17 Female	0.84
<b>Laterality</b>	96 Right 91 Left	14 Right 16 Left	0.70
<b>Presenting Visual Acuity (mean)</b>	0.61	0.60	0.27
<b>Category at diagnosis (%)</b>			
<b>1</b> Snellen 6/5 to 6/18 LogMAR -0.08 to 0.48	130 (69.5)	19 (63.3)	0.37
<b>2</b> Snellen 6/24 to 6/48 LogMAR 0.60 to 0.90	12 (6.4)	4 (13.3)	
<b>3</b> Snellen 6/60 to 3/60 logMAR 1.00 to 1.30	17 (9.1)	4 (13.3)	
<b>4</b> 2/60 or worse LogMAR 1.48 or worse	28 (15.0)	3 (10.0)	
<b>Tumour characteristics</b>			
<b>Height (mean)</b>	4.9mm	5.1mm	0.65
<b>Maximum basal diameter (mean)</b>	10.1mm	10.5mm	0.10
<b>Temporal or posterior pole</b>	107 (57.2%)	14 (46.7%)	0.28
<b>Distance to disc (mean)</b>	4.5mm	3.9mm	0.51
<b>Distance to fovea (mean)</b>	4.0mm	3.2mm	0.23
<b>Exudative Retinal Detachment</b>	74 (40.7%)	11 (36.7%)	0.84

**Appendix G:**

**Subgroup analysis of brachytherapy procedures done before 1<sup>st</sup> May 1994**

**Table A: Baseline characteristics of patients treated before and after 1<sup>st</sup> May 1994**

Variable	Early plaque Before 1 <sup>st</sup> May 1994 (n=45)	Later plaque After 1 <sup>st</sup> May 1994 (n=187)	P - value
<b>Age at diagnosis (median)</b>	54.2	58.0	0.11
<b>Gender</b>	20 Male 25 Female	88 Male 99 Female	0.75
<b>Laterality</b>	22 Right 23 Left	96 Right 91 Left	0.77
<b>Presenting Visual Acuity (mean)</b>	LogMAR 0.49 Snellen	LogMAR 0.61 Snellen	0.51
<b>Category at diagnosis (%)</b>			
<b>1</b> Snellen 6/5 to 6/18 LogMAR -0.08 to 0.48	33 (73.3)	130 (69.5)	0.52
<b>2</b> Snellen 6/24 to 6/48 LogMAR 0.60 to 0.90	5 (11.1)	12 (6.4)	
<b>3</b> Snellen 6/60 to 3/60 logMAR 1.00 to 1.30	2 (4.4)	17 (9.1)	
<b>4</b> 2/60 or worse LogMAR 1.48 or worse	5 (11.1)	28 (15.0)	
<b>Tumour characteristics</b>			
<b>Height (mean)</b>	5.2mm	4.9mm	0.15
<b>Maximum basal diameter (mean)</b>	12.1mm	10.1mm	<0.001
<b>Temporal or posterior pole</b>	21/45 (46.7%)	107/187 (57.2%)	0.20
<b>Distance to disc (mean)</b>	3.1mm	4.5mm	0.01
<b>Distance to fovea (mean)</b>	2.9mm	4.0mm	0.23
<b>Exudative Retinal Detachment</b>	20/45 (44.4%)	74/182 (40.7)	0.74
<b>Follow-up (median months)</b>	96.5	56.3	<0.001
<b>Follow-up Range</b>	21.5 to 258.8	6.4 to 175.8	

Prior to 1994 the department of Radiation Oncology designed and manufactured brachytherapy devices based on laboratory based dosing models. Following international discussion it was decided that the radiation doses used in all brachytherapy patients prior to that date were sub therapeutic. All subsequent patients received a dose of 80Gy to the tumour apex in keeping with internationally accepted guidelines. This analysis compares the baseline characteristics and outcomes of the early plaque cohort with those treated after 1<sup>st</sup> May 1994.

Maximum basal diameter was greater ( $p < 0.001$ ) and proximity to the optic disc was closer ( $p = 0.01$ ) in the early treatment group. Outcomes by early and late treatment are shown in

Table B:

**Table B: Outcomes**

	Early plaque Before 1 <sup>st</sup> May 1994 (n=45)	Later plaque After 1 <sup>st</sup> May 1994 (n=162)	P - value
<b>Final visual acuity (mean)</b>	1.51 Snellen <6/120	1.03 Snellen+ 6/60	0.02
<b>1 Snellen 6/5 to 6/18 LogMAR -0.08 to 0.48</b>	6 (14.3%)	60 (38.7%)	0.008
<b>2 Snellen 6/24 to 6/48 LogMAR 0.60 to 0.90</b>	3 (7.1%)	16 (10.3%)	
<b>3 Snellen 6/60 to 3/60 logMAR 1.00 to 1.30</b>	3 (7.1%)	9 (5.8%)	
<b>4 2/60 or worse LogMAR 1.48 or worse</b>	30 (71.4%)	70 (45.2%)	
<b>Recurrence</b>	15 (33.3%)	23 (14.2%)	0.008
<b>Enucleation</b>	13 (28.9%)	16 (9.9%)	0.003
<b>Metastases or death</b>	10 (22.2%)	21 (13.0%)	0.16

Final visual acuity, categorical visual outcomes, recurrence rates and enucleation rates were all significantly worse than those treated with therapeutic doses. Logistic regression models examining the prognostic factors for poor visual outcome of all brachytherapy patients revealed that early (sub therapeutic) plaque treatment was 3 times more likely to result in a poor visual outcome ( $p = 0.018$ ), 2.5 times more likely to result in recurrence ( $p = 0.041$ ), 2.9 times more likely to require enucleation ( $p = 0.037$ ). These results are not surprising and confirm that the doses were indeed likely to be sub therapeutic.

**Appendix H:**  
**Regression analysis**

**Logistic regression models for predictors of outcomes**

Logistic regression for **poor visual outcome if treated after 1<sup>st</sup> May 1994**

Prediction variable	Odds ratio	p-value	95% Confidence Interval	
Vision at diagnosis	1.89	0.03	1.06	3.36
1mm increase in tumour height	1.43	0.006	1.11	1.85
1mm increase in distance from fovea	0.69	0.006	0.53	0.90

Logistic regression analysis for patients treated **prior to 1<sup>st</sup> May 1994 (early plaque as prediction variable)**

Outcome	Odds ratio	p-value	95% Confidence Interval	
Poor vision	2.98	0.018	1.21	7.35
Tumour recurrence	2.46	0.041	1.04	5.86
Enucleation	2.86	0.037	1.06	7.69

**Cox models for predictors of outcomes**

Final Cox regression model for **recurrence** as outcome

Prediction variable	Hazard ratio	p-value	95% Confidence Interval	
1mm increase in distance from disc	0.69	0.016	0.51	0.93

Final Cox regression model for **enucleation** as outcome

Prediction variable	Hazard ratio	p-value	95% Confidence Interval	
1mm increase in tumour height	1.46	0.033	1.03	2.06

Final Cox regression model for **metastases or death** as outcome

Prediction variable	Hazard ratio	p-value	95% Confidence Interval	
Age at diagnosis	1.09	<0.001	1.05	1.23
1mm increase in tumour height	1.22	0.09	0.96	1.55