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Local tumour control and patient survival after ruthenium-106 brachytherapy for small choroidal melanoma

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SYNOPSIS

Ru-106 brachytherapy for small CM achieves tumour control and ocular survival in 83% and 96% of eyes, and metastasis and death rates are 4.8% and 2% at 5 years.

SHORT TITLE

Local control and survival in patients with small choroidal melanoma.

ABSTRACT

Aim: to report local tumour control, metastasis and survival rates of patients with small choroidal melanoma (CM) after treatment with ruthenium-106 (Ru-106) plaque brachytherapy.

Methods: retrospective case series of 353 consecutive eyes with small CM (thickness ≤2.5 mm and largest basal diameter ≤16 mm) treated with Ru-106 brachytherapy at the London Ocular Oncology Service, between October 2004 and May 2019.

Results: the final cohort included 310 eyes and tumour recurrence was observed in 52 (17%) eyes. Ocular retention rate was 96%. Metastatic disease and tumour-related death occurred in 18 (5.8%) and 12 (3.9%) patients, respectively. Metastases were diagnosed after a median of 54 (54±35; range 3.6-118) months from initial treatment. Kaplan-Meier estimates for tumour recurrence, melanoma-related metastases and survival were 17% (95% CI, 13.3%-22.9%), 4.8% (95% CI, 2.6%-8.5%) and 98% (95% CI, 94.4%-99.1%) at 5 years and 26% (95% CI, 18.3%-35.3%), 16% (95% CI, 8.7%-27.7%) and 92% (95% CI, 84.5%-95.7%) at 10 years, respectively. On multivariable analysis factors predictive for tumour recurrence included juxtapapillary location, larger plaque and final tumour thickness, and for metastasis exudative retinal detachment.

Conclusion: small CMs treated with Ru-106 brachytherapy show recurrence and death rates of 17% and 2% at 5 years and 26% and 8% at 10 years. As small CMs have better prognosis than large tumours, early treatment is the key for better survival outcomes.

KEY WORDS

Small choroidal melanoma, Ruthenium-106, tumour recurrence, enucleation, metastases, death.

What is already known on this topic

Survival outcomes of ruthenium-106 plaque brachytherapy for CM less than 2.5 mm in thickness remain ill-defined with only one study including 60 eyes specifically reporting outcomes for tumours of this size category.

What this study adds

This study shows that small CM after Ru-106 brachytherapy has a 5-year rate of recurrence of 17%, of distant metastases of 4.8%, of melanoma-related death of 2% and ocular retention of 96%. Factors predictive of tumour recurrence are juxtapapillary location, larger plaque and final tumour thickness.

How this study might affect research, practice or policy

This study provides new helpful data on recurrence and survival of small CM and will support clinicians in the decision-making process and patient counselling.

INTRODUCTION

Choroidal melanoma (CM) is the most common primary intraocular cancer of adulthood with an estimated incidence of 6-7 cases/million people/year (1) and more than 50% risk of metastasis at 10 years from initial diagnosis in large melanomas with adverse genetic profile (2). Of CMs, 30% are small (3, 4) and 11% of uveal melanomas with systemic metastases at the time of tumour diagnosis are stage T1 of the American Joint Committee on Cancer classification (AJCC, 8th edition) (5, 6).

The approach of initial observation of small uveal melanocytic lesions and treatment in case of growth or signs of malignant transformation has seen a shift in the last decade to early intervention to reduce the risk of metastasis and death (7), as tumour size is a major prognostic factor for survival (6). Theoretical and clinical studies suggest that uveal melanoma micro-metastases start several years before treatment (8), thus explaining the development of metastatic disease in 50% of cases at 10 years from successful primary treatment (9). This is confirmed by circulating tumour cells and tumour-derived DNA and by the transition from low to high risk genetic profile (10, 11, 12). 27% of small CMs have monosomy 3 which predicts high metastatic risk; however, the 5-year absolute mortality risk for small CMs is lower than large CMs with monosomy 3 (23% versus 50%), hence the shift to early treatment to prevent the development of genetic characteristics associated with systemic dissemination (13).

A handful of studies explored the outcomes of plaque radiotherapy for small CM, and the lack of a well-defined size-based classification system (two different systems used: Collaborative Ocular Melanoma Study (COMS) and AJCC) limits comparisons between these. Herein, we report the tumour recurrence, ocular retention, metastasis and death rates for patients with small CM treated with ruthenium-106 (Ru-106) episcleral plaque brachytherapy with a radiation dose prescribed to the tumour apical height.

METHODS

This study was conducted at the London Ocular Oncology Service based at Moorfields Eye Hospital and St Bartholomew's Hospital. The study was approved by the clinical audit department (number 53) of Moorfields Eye Hospital and no approval from institutional ethic committee for outcome analysis was required. The research involved retrospective information collection without identifiable private information and was conducted according to the principles of the Declaration of Helsinki. Informed consent for research was obtained from all patients prior to treatment.

Patients presenting to our service between October 2004 and May 2019 with small CM having thickness ≤2.5 mm and largest basal diameter (LBD) ≤16 mm on B scan ultrasound (US) (according to the Collaborative Ocular Melanoma Study criteria) and with ≥3 risk factors for future growth or documentation of recent growth were included. Risk factors for growth were: thickness ≥2 mm, subretinal fluid (SRF), symptoms of reduced vision, orange pigment, proximity to the optic disc (≤3 mm) (14). Suspicious lesions were monitored every 4 months to look for any growth or new risk factors. Tumours were retrospectively staged according to the 8th edition of the AJCC TNM (Tumour Node Metastasis) classification (15).

Data collected for each patient included sex, age, ethnicity, personal and family history of cancer, predisposing factors (ocular melanocytosis and choroidal naevus), visual acuity and tumour features. All patients underwent a comprehensive ophthalmological examination including Snellen best corrected visual acuity (BCVA), intraocular pressure, slit lamp biomiscroscopy, dilated indirect fundoscopy, colour (Topcon Corporation, Tokyo, Japan) or pseudocolour (Optos plc, Dunfermline, UK) fundus photography, Optical Coherence Tomography (OCT Spectralis, Heidelberg Engineering, Heidelberg, Germany) or Enhanced Depth Imaging OCT (EDI-OCT, Spectralis), fundus autofluorescence (Optos or Spectralis) and B-scan ocular US (ACUSON S 2000, Siemens Healthcare, Germany).

Tumour LBD was defined by indirect ophthalmoscopy and B-scan US and tumour thickness by B-scan US or OCT when the internal scleral surface was visible. Indirect ophthalmoscopy and fundus photographs were used to estimate the distance from the posterior tumour margin to the optic disc and foveola, to evaluate the growth, the presence of SRF or exudative retinal detachment (SRF extending beyond one disc diameter from the tumour margin) and of orange pigment.

Exclusion criteria

We excluded patients with a follow-up of less than 3 months or insufficient information, those who received other treatments such as trans-pupillary thermotherapy (TTT) or photodynamic therapy (PDT) prior to plaque, and with tumours involving the ciliary body and/or the iris.

Treatment protocol

Patients were treated with Ru-106 plaque brachytherapy (Eckert & Ziegler BEBIG GmbH, Berlin, Germany) and the plaque size (12, 15 or 20 mm) and shape (circle or notched) were recorded. A scleral dose of 250–350 Gray (Gy) and apex dose of 80–100 Gy were prescribed, using the manufacturer's ASMW (Amt fur Standardisierung Messwesen und Warenprufung) specifications. Treatment times were calculated according to the manufacturer's plaque simulator data. The prescription point for the sclera was tumour height plus 1 mm in order to include the scleral thickness.

Regarding our surgical technique, the tumour anterior, lateral and posterior (where possible) margins were identified by transpupillary transillumination or indentation. The sclera was marked with methylene blue in correspondence of the tumour margins. The anterior margin of a transparent plastic template ('dummy' plaque) was sutured to the sclera with its anterior edge at least 2 mm beyond with the ink mark on the sclera. Correct positioning was confirmed by indirect

ophthalmoscopy and repeating transillumination. The plaque was considered to be in good position if the light from the transilluminator was located at least 2 mm from all tumour margins. The template was then replaced with the radioactive plaque. Any overlying extraocular muscles preventing an accurate positioning of the plaque over the tumour were disinserted. Before muscle disinsertion, sutures were placed in the muscles and the knot-to-limbus distances were measured and recorded. After positioning the plaque the disinserted muscles were returned to their correct anatomic position on a 'hang-back' technique.

Follow-up

Patients were reviewed one month after treatment, every four months in the first year, every six months in the second and third years, and annually thereafter. Follow-up data included tumour recurrence and its treatment, melanoma-related metastases and death. Tumour recurrence was labeled as follows: 'marginal' if unequivocal expansion of any tumor margin when comparing the ophthalmoscopic appearances with previous photographs; 'vertical' if increase in thickness of at least 0.5 mm on US (overall or nodular); 'diffuse' if both marginal and vertical growth; 'new satellite lesions'; and 'no thickness reduction'. Time to tumour recurrence was calculated from the date of primary treatment.

Metastatic surveillance

At the time of primary diagnosis patients were referred to a medical oncologist and underwent systemic staging including abdominal and pelvis imaging or whole-body PET/CT. Liver imaging by means of US or magnetic resonance imaging (MRI) was repeated six monthly and was lifelong. Liver metastases were staged with imaging of other organs and confirmed through biopsy or documented progression. The time interval between initial treatment and metastasis detection was recorded.

For deceased patients the date and cause of death were recorded. For patients that stopped coming to our institution information on metastasis and death was gathered by contacting the patients, their families and physicians.

Statistical analysis

Statistical analysis was performed using Microsoft Excel (version 16.41) and Stata software (version 14.1 StataCorp LP, TX, USA). Data are presented as mean ± standard deviation (SD) when normally distributed, or as median (interquartile range (IQR) and range) when not. Hypothesis testing used two-tailed statistics and a significance was defined by p value of ≤0.05. Categorical variables were analyzed with chi-square and Fisher's exact tests. Kaplan-Meier methods were calculated for time to event and used to estimate the cumulative probability of tumour recurrence, secondary enucleation, metastasis and death. Univariate analyses using the Cox proportional hazards model were performed to identify factors predictive of tumour recurrence, enucleation, metastases and death based on clinical features at presentation and treatment parameters. Subsequent multivariate analysis was performed using the forward stepwise method for factors deemed statistically significant at p ≤0.05 in the univariate analysis, to determine which combination of factors best related to the studied event. Hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated for each risk factor. Patients were censored if death did not occur by the time of last follow-up or occurred as a result of another cause.

RESULTS

The data of three hundred fifty-three eyes were extracted. A total of 43 patients were excluded due to lack of follow-up information.

Three hundred and ten eyes from three hundred and ten patients with a diagnosis of small CM (298 stage T1a, 2 stage T1c, 10 stage T2a) were included in the analysis, with mean age of 58±14 (median 60; range 25-89) years and median follow-up (from date of treatment to date of last visit) of 57 (mean 64±36; range 3.4-171) months. 296 (96%) patients were white and 160 (52%) were male. 44 (14%) patients had a second cancer in addition to the CM, and 82 (27%) had family history of cancer. Tumour location was posterior pole for 145 tumours (47%), peripheral for 95 (30%), juxta-papillary for 61 (20%) and both posterior pole and periphery for 9 (3%). Patient demographics and baseline tumour characteristics are summarized in table 1. Visual acuity and treatment-related side effects from this cohort have been reported separately (submitted).

Table 1.

Features	N (%)
Age at diagnosis (years), median (mean, range)	60 (58, 25-89)
Ethnicity	
White British	256 (83)
White other	40 (13)
Asian	1 (0.3)
Unknown	13 (4)
Gender	
Male	160 (52)
Female	150 (48)
Laterality	
Right	163 (53)
Left	147 (47)
Ocular symptoms at presentation (can have more than one)	194 (63)
Absent	116 (37)
Blurred vision	105 (54)
Photopsia	93 (48)
Floaters	7 (3.6)
Visual field defect	27 (14)
Metamorphopsia	13 (6.7)
Ocular pain	1 (0.5)
Symptom duration (months), median (mean, range)	3 (3.6, 0.25-24)
Follow-up duration (months), median (mean, range)	57 (64, 3.4-171)
Distance to optic disc (mm), median (mean, range)	3 (3.4, 0-15)
Posterior pole tumours	3 (3±1.8, 0-8)
Juxta-papillary tumours	0 (0.4±0.7, 0-3)
Peripheral tumours	5 (5.9±3.2, 1.5-15)
Posterior pole and periphery tumours	3 (3.1±1.4, 1-6)
Distance to foveola (mm), median (mean, range)	2.5 (3.1, 0-15)
Posterior pole tumours	0.5 (1.2±1.4, 0-6)
Juxta-papillary tumours	3 (2.5±1.7, 0-6)
Peripheral tumours	6 (6.7±2.9, 3.5-15)
Posterior pole and periphery tumours	0.5 (0.9±1.1, 0-3)
Location	
Posterior pole	145 (47)
Juxta-papillary	61 (20)
nasal	20
temporal	23
inferior	7
superior	11
Periphery	95 (30)
nasal	35
temporal	24
inferior	6
superior	30
Posterior pole and periphery	9 (3)
Subretinal fluid	274 (88)
localized	246
exudative retinal detachment	28
Thickness (mm), median (mean, range)	2 (1.9, 0.4-2.5)
LBD (mm), median (mean, range)	7.1 (7.5, 2.9-16)

2.9 ≤LBD< 6 mm	76 (25)
6 ≤LBD< 9 mm	159 (51)
9 ≤LBD< 12 mm	60 (19)
12 ≤LBD≤ 16 mm	15 (5)
Shape	
dome	282 (91)
collar-stud	3 (1)
diffuse	25 (8)
TNM stage	
T1a	298 (96)
T1b	-
T1c	2 (0.7)
T2a	10 (3.2)
Colour	
pigmented	235 (76)
amelanotic	25 (8)
mixed pigmentation	50 (16)
Personal history of other cancer	44 (14)
1 type of cancer	38 (12)
2 types of cancer	6 (2)
Family history of cancer	82 (27)
Risk factors	129 (42)
Ocular melanocytosis (naevus of Ota)	1 (0.3)
Choroidal naevus	128 (41)
Time between choroidal naevus and CM diagnosis (months), median (mean, range)	36 (56, 0-228)

Treatment

All eyes were treated with Ru-106 plaque, the only radioisotope used in our centre. Plaque size was 12 mm in 5 eyes (1.6%), 15 mm in 43 eyes (14%) and 20 mm in 262 eyes (84%); plaque shape was notched for 91 (29%) tumours and circular for the remaining cases. A radiation apex dose of 100 Gy was given to 249 (80%) eyes. Median time between tumour diagnosis and treatment was 30 (range 3-310) days.

Tumour recurrence

There were 52 eyes (17%) that developed tumour recurrence after a median of 20 (mean 30±28; range 4-122) months from treatment (table 2).

Table 2.

	N (%)
Tumour recurrence (eyes)	52 (17)
Number of recurrences, mean (median, range)	1.3 (1, 1-4)
Recurrence type:	
- vertical	13 (25)
- marginal	29 (56)
- diffuse	5 (9.6)
- new satellite lesion	1 (1.9)
- no thickness reduction	1 (1.9)
- not specified	3 (5.8)
Time of onset of recurrence, months, median (mean, range)	20 (30, 4-122)
Recurrence based on tumour location:	
- Posterior pole	23 (44)
- Juxtapapillary	21 (40)
- Peripheral	8 (15)

Recurrence treatment:	
- 2nd Plaque	4
- PBRT	14
- TTT	
o alone	19
o combined with 2nd plaque	3
o combined with PBRT	3
o combined with PBRT and enucleation	1
o combined with enucleation	6
- Enucleation	13
o after failed plaque	6
o after failed TTT	6
o after failed PBRT	1

The pattern of recurrence was more commonly vertical (13 eyes) and marginal (29 eyes), and was mostly observed in posterior pole (23 eyes) and juxta-papillary (21 eyes) tumours. Recurrence treatment consisted of further radiotherapy in 18 (35%) eyes, of whom 4 receiving a second plaque and 14 Proton Beam Radiotherapy (PBRT), TTT alone in 19 (37%) and combined with other treatments in 13 eyes.

Kaplan-Meier estimates of tumour recurrence were 12%, 17% and 26% at 3, 5 and 10 years, respectively (Table 3 and figure 1A).

Table 3.

		Kaplan-Meier estimates, no. of affected patients/no. of unaffected patients (%) [95%CI]					
Outcomes	**N (%)**	**1 yr**	**2 yr**	**3 yr**	**5 yr**	**10 yr**	**14 yr**
Local tumour recurrence	52 (16.8)	16/282 (5.3) [3.3-8.5]	29/246 (9.8) [6.9-14]	35/196 (12) [8.9-17]	45/125 (17) [13.3-23]	51/15 (26) [18.3-35]	52/1 (31) [20.1-47]
Enucleation	13 (4.2)	1/302 (0.3) [0.05-2.3]	1/280 (0.3) [0.05-2.3]	3/228 (1.1) [0.3-3.3]	5/159 (2) [0.8-4.9]	12/24 (11) [5.4-20]	13/2 (55) [13.4-99]
Melanoma-related metastasis	18 (5.8)	2/302 (0.7) [0.2-2.6]	4/280 (1.3) [0.5-3.5]	6/228 (2.1) [1-4.7]	11/157 (4.8) [2.6-8.5]	18/24 (16) [8.7-28]	18/2 (16) [8.7-28]
Death (all causes)	35 (11.3)	1/303 (0.3) [0.1-2.3]]	4/280 (1.3) [0.5-3.5]	8/229 (2.9) [1.5-5.8]	15/159 (6.6) [4-11]	32/26 (22) [15.5-31]	35/2 (35) [22.-52]
Melanoma-related death	12 (3.9)	1/303 (0.3) [0.1-2.3]	2/280 (0.7) [0.2-2.6]	2/229 (0.7) [0.2-2.6]	5/160 (2) [0.9-5.6]	11/25 (8) [4.3-16]	12/2 (12) [5.7-25]

Factors best predictive of tumour recurrence on multivariate analysis were final tumour thickness (HR 3.4, 95% CI, 2.26-5.12, p<0.001), closer distance to optic disc (HR 0.58, 95% CI, 0.41-0.82, p=0.002) and 20 mm plaque size (p<0.001) (table 4, supplementary material).

Secondary enucleation

In this study 13 (4.2%) eyes underwent enucleation due to tumour recurrence after a median of 61 (mean 68, range 9-164) months from primary treatment, resulting in an ocular retention rate of 96%.

Kaplan-Meier 5-year and 10-year secondary enucleation rates were 2% and 11%, respectively (table 3 and figure 1B), and the factors predictive of enucleation on multivariate analysis were baseline BCVA (HR 4.13, 95% CI, 1.09-15.74, p=0.037), location closer to the fovea (HR 0.61, 95% CI, 0.40-0.91, p=0.016) and history of second cancer (HR 9.73, 95% CI, 1.94-48.75, p=0.006) (table 4, supplementary material).

Metastasis and death

Distant metastases developed in 18 (5.8%) patients, and were hepatic in 14, multi-organ (liver, spleen, bone, lungs) in two, and extra-hepatic (kidney, bone marrow) in two. Among these, 4 patients had also a second cancer, of whom two breast cancer, one mandibular melanoma and one prostate cancer, and 5 had developed tumour recurrence. No patients had systemic metastases synchronous with the primary tumour diagnosis. The metastasis-free interval, defined as median time between CM diagnosis and metastatic disease detection, was 54 (54±35; range 4-118) months. At the time of the analysis 35 (11%) patients had died, of whom 16 (5.2%) of unknown causes, 12 (3.9%) of metastatic disease, 2 (0.6%) of metastases from another cancer (esophageal and renal

cancer) and 5 (1.6%) of other causes. The median survival from diagnosis of metastatic disease was 6.7 (9.6±7.5; 2.2-22) months. At the end of the study 6 patients were alive with metastases. Considering all causes of death, the median survival from tumour diagnosis was 64 (66±33; 5.8-131) months.

Kaplan-Meier estimates for distant metastases were 4.8% and 16% at 5 and 10 years, respectively, and the 5-year and 10-year survival rates were 98% and 92%, respectively (table 3 and figure 1C-E). Factors predictive of metastases on univariate analysis were collar-stud shape (HR 30.65, 95% CI, 3.37-278.79, p=0.002), baseline (HR 3.95, 95% CI, 1.02-15.31, p=0.047) and final tumour thickness (HR 2.41, 95% CI, 1.4-4.15, p=0.002) and exudative retinal detachment (HR 4.19, 95% CI, 1.3-13.51, p=0.016), and on multivariate analysis exudative retinal detachment (HR 19.15, 95% CI, 3.31-110.65, p=0.001). 22% of patients with metastasis had developed tumour recurrence. However, no correlation between tumour recurrence and metastasis was observed (p=0.83) (table 5, supplementary material).

Factors predictive of death reaching statistical significance on multivariate analysis were older age (HR 1.08, 95% CI, 1.04-1.13, p<0.001), final tumour thickness (HR 1.92, 95% CI, 1.28-2.87, p=0.001) and metastasis (HR 8.34, 95% CI, 3.8-18.32, p<0.001) (table 5, supplementary material).

DISCUSSION

Our study reports the rates of tumour recurrence, secondary enucleation, distant metastases and melanoma-related death for a large cohort of CMs less than 2.5 mm in thickness treated with primary Ru-106 plaque brachytherapy. Few previous studies with limited number of cases (13, 16, 17, 18, 19, 20, 21, 22, 23, 24) specifically focused on outcomes of brachytherapy for tumours of this size category, of which only two addressed Ru-106 (22, 23).

In our study 17% of eyes, more frequently affected by posterior pole and juxta-papillary tumours, developed tumour recurrence that was managed conservatively with TTT or additional radiotherapy in most cases (13%). Tumour recurrence was correlated with final tumour thickness ($p<0.001$) and larger plaque size ($p<0.001$). Final tumour thickness may be an indicator of recurrence. The only prior study on Ru-106 outcomes in 60 eyes with small CM (22) found lower recurrence rates (9-13% at 5 years and 13-15% at 10 years), however the included tumours were smaller as their LBD was less than 10 mm, while 24% of eyes in our cohort had LBD greater than 9 mm. Damato et al (23) in their study showed significantly lower recurrence rates (1% at 2 years, 2% at 5 years, 3% at 7 years) with Ru-106 plaque brachytherapy for tumours having median thickness of 3.2 mm (126 tumours less than 2.5 mm); however, it is worth mentioning some key dissimilarities: their cohort included also tumours involving the ciliary body; some patients received adjuvant TTT or photocoagulation 6 months after plaque to prevent tumour recurrence; patients treated with notched plaques were not included; all surgeries were performed by a single highly experienced surgeon, while in our series surgeries were performed by several surgeons with heterogenous levels of experience. Conversely, the Small Fatal Choroidal Melanoma Study (19) showed higher tumour recurrence rates (26%), but included also tumours managed with other primary treatment modalities (PBRT, TTT) that in half of cases were observed before treatment.

Studies on Palladium-103 (Pd-103) and Iodine-125 (I-125) showed lower tumour recurrence rates, specifically for Pd-103 of 0% at 5 years (for tumours <2.4mm in thickness and <10 mm in LBD) (18) and for I-125 of 6.5% at 5 years and 11% at 10 years (16, 17). A possible explanation for this difference could be that Ru-106 beta-radiation dose is lower at the edges of the plaque compared to gamma-radiation emitting I-125 (25-26).

Secondary enucleation was necessary in 4.2% of eyes after failure of conservative salvage therapies. Our Kaplan-Meier estimates for enucleation at 5 and 10 years were 2% and 11%, respectively. These figures are in keeping with both the Small Fatal Choroidal Melanoma Study (19) where enucleation was performed in 4.4% of cases, and with studies on I-125 where enucleation rates ranged between 0.7% at 3 years (16) and 4% at 5 years (17, 20). History of second cancer was correlated to secondary enucleation and this suggests that genetic abnormalities might predispose to more aggressive local tumour behaviour and development of multiple cancers.

Distant metastases developed in 5.8% of patients, most commonly affecting the liver. Our metastatic rates at 5 and 10 years were 4.8% and 16% respectively, which are in line with the previously reported 5-year risk of metastasis for CM of thickness <3 mm ranging from 4.5% (17) to 16% (19, 27). 22% of patients with metastasis had developed tumour recurrence which is a known risk factor for metastatic disease (28). However, we did not observe a statistically significant correlation between tumour recurrence and metastasis, although this could be related to the small number of study eyes.

Theoretical models suggest that the smallest CMs able to metastasize are ≥1 mm in thickness and ≥ 3 mm in LBD (8). The two smallest previously reported metastasizing CMs have thickness of 1.7 mm (29) and LBD of 3 mm (19). In our cohort the smallest metastasizing CM of a patient alive at the time of analysis had thickness of 1.1 mm and LBD of 4.9 mm (figure 2), while the smallest metastasizing and deadly CM had thickness of 1.3 mm and LBD of 5.4 mm.

By the end of the study 3.9% of patients died of metastatic CM after a median survival from primary tumour diagnosis of 64 months (5.3 years) and from metastasis detection of 6.7 months. Our melanoma-specific mortality rate is in line with the previous studies where it ranges between 0% at 3 years (16, 18), to 3.8-3.9% at 5 years (17, 20) and 3-8% at 10 years (22, 17). Only the COMS study

reported a significantly lower (1%) 5-year melanoma-specific mortality rate as it included also suspicious choroidal lesions that were not treated as they did not grow, presumably carrying a lower metastatic risk (21). A study would be confounded by lower rates of recurrence and metastasis if choroidal naevi were misdiagnosed as CMs (23, 30).

New treatment modalities are emerging for the treatment of small CM and high-risk indeterminate melanocytic lesions. In particular, a new promising therapy currently investigated in clinical trials is Bel-sar (belzupacap sarotalocan, AU-011), a recombinant virus-like drug conjugate that binds to uveal melanoma cells through modified heparan sulfate proteoglycans and when activated by 690 nm wavelength light causes a selective immunogenic death of uveal melanoma cells (31). This could have the advantage of reducing collateral damage to the structures adjacent to the tumour minimizing vision loss. In animal models Bel-sar induced long-term antitumour immunity that increased when combined with checkpoint inhibitors (32). The long-term effects of Bel-sar still have to be defined, and will have to be benchmarked against conventional radiotherapy treatments (plaque and PBRT) for tumours of this size category, hence the importance of reporting our results. The use of PDT and TTT in small CM is widely documented in the literature, but both techniques are used only sparsely in selected cases as first line treatment. Despite a gentler side effect profile, they are associated with higher rates of tumour recurrence, of up to 54% (33) for PDT and 56% for TTT (34), proving they are not effective as standalone treatments.

Limitations of our study include the retrospective nature and lack of cytopathology and molecular prognostication that could have provided useful correlation with tumour metastatic behaviour. For instance, for cases that were initially observed for growth and that developed distant metastases it is difficult to ascertain whether the poor prognosis was caused by treatment delay or by tumour

high-risk genetic profile. Reassuringly, Singh et al have indicated that smaller melanomas with a lower clinical risk on their predictive model could be observed to document growth without an increase in metastatic risk before instigating potentially sight threatening treatment (30). Other observations suggest that the growth rate of choroidal melanocytic lesions is a critical factor in predicting transformation in presumed incipient CM (35). In our cohort 40% of CMs arose from choroidal naevi, many of whom were observed for change locally (median time 36 months) before prompting a referral to our center; therefore we are unable to ascertain if some of these cases were incipient CM when first detected and would have benefited from earlier treatment. Lastly, outcomes for metastases and death were reported by patients and their families, and for some patients that died of unknown causes the death may be related to metastatic CM, hence the melanoma-specific metastatic and death rates might have been underestimated. Due to a limited number of patients being followed-up for 10 years or longer, the 10-year data need to be interpreted with caution. Points of strengths are the long follow-up and the homogeneity of the sample for size and treatment due to the strict inclusion criteria.

In conclusion, our study shows that Ru-106 brachytherapy for small CM achieves tumour control in 83% and eye retention rate in 96% of cases, and is associated with 4.8% and 16% melanoma-related metastases and 2% and 8% melanoma-related death rates at 5 and 10 years, suggesting that small tumours can be lethal. The smallest metastasizing CM in this study had thickness of 1.1 mm and LBD of 4.9 mm. Our treatment outcome data will act as a benchmark for future studies, especially in new modalities of treatment, and support clinicians when counselling their patients.

TABLES

Table 1. Baseline demographic data and tumour characteristics of the study cohort (n=310). LBD: largest basal diameter; CM: choroidal melanoma.

Table 2. Summary of tumour recurrence and management of the study cohort (n=310). PBRT: Proton Beam Radiotherapy; TTT: trans-pupillary thermotherapy.

Table 3. Kaplan-Meier analysis of tumour recurrence, enucleation, melanoma-related metastasis, death from all causes and melanoma-related death for Ru-106 plaque radiotherapy for small choroidal melanoma (n=310).

Table 4. Supplementary material. Clinical features associated with tumour recurrence and secondary enucleation after Ru-106 plaque brachytherapy for patients with small choroidal melanoma (n=310). Bold values indicate statistical significance.

Table 5. Supplementary material. Clinical features associated with metastatic disease and death after Ru-106 plaque brachytherapy for patients with small choroidal melanoma (n=310). LBD: largest basal diameter. Values in bold indicate statistical significance.

FIGURES

Figure 1. Kaplan-Meier estimation of tumour recurrence (A), secondary enucleation (B), metastasis (C) and survival (D, E).

Figure 2. Multimodal imaging of small CM. (A) wide-field pseudocolour fundus image, (B) fundus autofluorescence and (C) EDI-OCT at presentation of the smallest metastasizing CM of our cohort of a patient alive at the time of analysis. The tumour was juxtapapillary, dome shaped, had thickness of 1.1 mm and largest basal diameter of 4.9 mm, orange pigment and subretinal fluid. Infero-temporal peripheral bullous retinoschisis.

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CONFLICT OF INTEREST

None of the authors has any conflicts of interest to disclose.

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CONTRIBUTORS

Study concept and design: BG and MSS. Acquisition, analysis and interpretation of data: all authors. Drafting of the manuscript and critical revision for important intellectual content: all authors. Final approval of the version to be published: all authors.

ETHICS STATEMENT

This study was carried out in compliance with the Declaration of Helsinki and was approved by the clinical audit department (number 53) of Moorfields Eye Hospital.

REFERENCES

1. Egan KM, Seddon JM, Glynn RJ, Gragoudas ES, Albert DM. Epidemiologic aspects of uveal melanoma. *Surv Ophthalmol*, 1988;32(4):239-251.

2. Gragoudas E, Li W, Goitein M, Lane AM, Munzenrider JE, Egan KM. Evidence- based estimates of outcome in patients irradiated for intraocular melanoma. *Arch Ophthalmol*, 2002;120(12):1665-1671.

3. The collaborative ocular melanoma study group. The COMS randomized trial of Iodine 125 brachytherapy for choroidal melanoma, III: initial mortality findings. COMS report n.18. *Arch Ophthalmol*, 2001; 199:969-82.

4. McLean IW, Foster WD, Zimmerman LE. Uveal melanoma: location, size, cell type, and enucleation as risk factors in metastasis. *Hum Pathol*, 1982;13:123-132.

5. Gershenwald JE, Scolyer RA, Hess KR, et al. Melanoma staging: evidence-based changes in the American Joint Committee on Cancer eighth edition cancer staging manual. CA *Cancer J Clin*, 2017;67(6):472–492.

6. Garg G, Finger PT, Kivelä TT, Simpson ER, Gallie BL, Saakyan S, Amiryan AG, Valskiy V, Chin KJ, Semenova E, Seregard E, Fili M, Wilson M, Haik B, Caminal JM, Catala-Mora J, Gutierrez C, Pelayes DE, Folgar AM, Jager MJ, Dogrusoz M, Luyten GPM, Singh AD, Suzuki S; AJCC Ophthalmic Oncology Task Force. Patients presenting with metastases: stage IV uveal melanoma, an international study. *Br J Ophthalmol*, 2022;106(4):510-517.

7. Boldt H C, Binkley E. Treating Small Choroidal Melanoma. Smaller Is Better. *JAMA Ophthalmol*, 2018; 1:136(12):1333-1334.

8. Eskelin S, Pyrhönen S, Summanen P, Hahka-Kemppinen M, Kivelä T. Tumor doubling times in metastatic malignant melanoma of the uvea: Tumor progression before and after treatment. *Ophthalmol*, 2000;107(8):1443-9.

9. Kujala E, Makitie T, Kivela T. Very long-term prognosis of patients with malignant uveal melanoma. *Invest Ophthalmol Vis Sci*, 2003;44:4651–9.

10. Anand K, Roszik J, Gombos D, Upshaw J, Sarli V, Meas S, Lucci A, Hall C, Patel S. 2019. Pilot study of circulating tumor cells in early-stage and metastatic uveal melanoma. *Cancers*, 2019;11, 856.

11. Beasley A, Isaacs T, Khattak MA, Freeman JB, Allcock R, Chen FK, Pereira MR, Yau K, Bentel J, Vermeulen T, Calapre L, Millward M, Ziman MR, Gray ES. Clinical application of circulating tumor cells and circulating tumor DNA in uveal melanoma. *JCO Precis Oncol*, 2018; 2. PO.17.00279.

12. Francis JH, Canestraro J, Brannon AR, Barker CA, Berger M, Shoushtari AN, Abramson DH. Association of plasma circulating tumour DNA with diagnosis of metastatic uveal melanoma. *JAMA Ophthalmol*, 2021; 139(11):1244-1245.

13. Hussain RN, Coupland SE, Kalirai H, Taktak AFG, Eleuteri A, Damato BE, Groenewald C, Heimann H. Small High-Risk Uveal Melanomas Have a Lower Mortality Rate. *Cancers*, 2021;13(9):2267.

14. Shields CL, Shields JA, Kiratli H, De Potter P, Cater JR. Risk factors for growth and metastasis of small choroidal melanocytic lesions. *Ophthalmol*, 1995; 102(9):1351-1361.

15. AJCC Ocular Oncology Task Force. International Validation of the American Joint Committee on Cancer's 7th Edition Classification of Uveal Melanoma. *JAMA ophthalmology*. 2015;133:376-383. 17.

16. Yupari R J, Bena J, Wilkinson A, Suh J, Singh A. Small choroidal melanoma: outcomes following apical height dose brachytherapy. *Br J Ophthalmol*, 2020;0:1-5.

17. Shields CL, Sioufi K, Srinivasan A, Di Nicola M, Masoomian B, Barna LE, Bekerman VP, Say EAT, Mashayekhi A, Emrich J, Komarnicky L, Shields JA. Visual Outcome and Millimeter Incremental Risk of Metastasis in 1780 Patients With Small Choroidal Melanoma Managed by Plaque Radiotherapy. *JAMA Ophthalmol*, 2018;136(12):1325-1333.

18. Semenova E, Paul T. Finger P T. Palladium-103 Radiation Therapy for Small Choroidal Melanoma. *Ophthalmol*, 2013; 120(11):2353-7.

19. Jouhi S, Jager MJ, de Geus SJR, Desjardins L, Eide NA, Grange JD, Kiilgaard JF, Seregard S, Midena E, Parrozzani R, Caujolle JP, Rospond-Kubiak I, Kivela TT. The small fatal choroidal melanoma study. A survey by the European Ophthalmic Oncology Group. *Am J Ophthalmol*, 2019;202:100-108.

20. Sobrin L, Schiffman JC, Markoe AM, Murrau TG. Outcomes of Iodine 125 plaque radiotherapy after initial observation of suspected small choroidal melanomas. A pilot study. *Ophthalmol*, 2005; 122(10):1777-83.

21. Mortality in patients with small choroidal melanoma. COMS report no. 4. The Collaborative Ocular Melanoma Study Group. *Arch Ophthalmol*, 1997;115(7):886-93.

22. Jouhi S, Heikkonen J, Reijonen V, Raivio V, Täll M, Kivelä TT. Brachytherapy of choroidal melanomas less than 10 mm in largest basal diameter. Comparison of 10-mm and 15-mm Ruthenium Plaques. *Ophthalmol*, 2021; 128 (1):140-151.

23. Damato B, Patel I, Campbell IR, Mayles HM, Errington RD. Local tumour control after Ru-106 brachytherapy of choroidal melanoma. Int J Radiation Oncology Biol Phys, 2005;63(2):385-391.

24. Singh AD, Grossniklaus HE. What's in a name? Large choroidal nevus, small choroidal melanoma, or indeterminate melanocytic tumor. *Ocul Oncol Pathol*, 2021;7:235-238.

25. Shields CL, Naseripour M, Cater J, Shields JA, Demirci H, Youseff A, et al. Plaque radiotherapy for large posterior uveal melanomas (> or = 8 mm thick) in 354 consecutive patients. *Ophthalmol*, 2002;109:1838-49.

26. Char DH, Kroll S, Phillips TL, Quivey JM. Late radiation failures after iodine 125 brachytherapy for uveal melanoma compared with charged-particle (proton or helium ion) therapy. Ophthalmol, 2002;109:1850-4.

27. Diener-West M, Hawkins BS, Markowitz JA, Schachat AP. A review of mortality from choroidal melanoma, II: a meta-analysis of 5-year mortality rates following enucleation, 1966 through 1988. *Arch Ophthalmol*, 1992;110:245–250.

496 28. Ophthalmic Oncology Task Force. Local recurrence significantly increases the risk of metastatic
497 uveal melanoma. *Ophthalmol*, 2016;123(1):86-91.
498 29. Robertson DM. Small choroidal melanomas treated with transpupillary thermotherapy and
499 cryotherapy. *Arch Ophthalmol*, 2008;126(8):1156–1157.
500 30. Singh AD, Raval V, Wrenn J, Zabor EC. Small choroidal melanoma: outcomes after surveillance
501 versus immediate treatment. *Am J Ophthalmolol*, 2022;241:47-56.
502 31. Ma S, Huis In't Veld RV, Houy A, Stern MH, Rich C, Ossendorp FA, Jager MJ. In Vitro Testing of
503 the Virus-Like Drug Conjugate Belzupacap Sarotalocan (AU-011) on Uveal Melanoma Suggests BAP1-
504 Related Immunostimulatory Capacity. Invest Ophthalmol Vis Sci. 2023 Jun 1;64(7):10.
505 32. Huis In't Veld RV, Ma S, Kines RC, Savinainen A, Rich C, Ossendorp F, Jager MJ. Immune
506 checkpoint inhibition combined with targeted therapy using a novel virus-like drug conjugate
507 induces complete responses in a murine model of local and distant tumours. *Cancer Immunol*
508 *Immunother*, 2023;72(7):2405-2422.
509 33. Roelofs KA, Fabian ID, Arora AK, Cohen VML, Sagoo MS. Long-term outcomes of small pigmented
510 choroidal melanoma treated with primary photodynamic therapy. Ophthalmol Retina,
511 2021;5(5):468-478.
512 34. Spire M, Devousassoux MS, Kodjikian L, Janin-Magnificat H, Fleury J, Grange J. Primary
513 transpupillary thermotherapy for 17 small posterior pole uveal melanomas. *Am J Ophthalmol*,
514 2006;141(5):840-849.
515 35. Jouhi S, Al-Jamal RT, Tall M, Eskelin S, Kivela T. Presumed incipient choroidal melanoma:
516 proposed diagnostic criteria and management. *British J Ophthalmol*, 2021;0:1-6.

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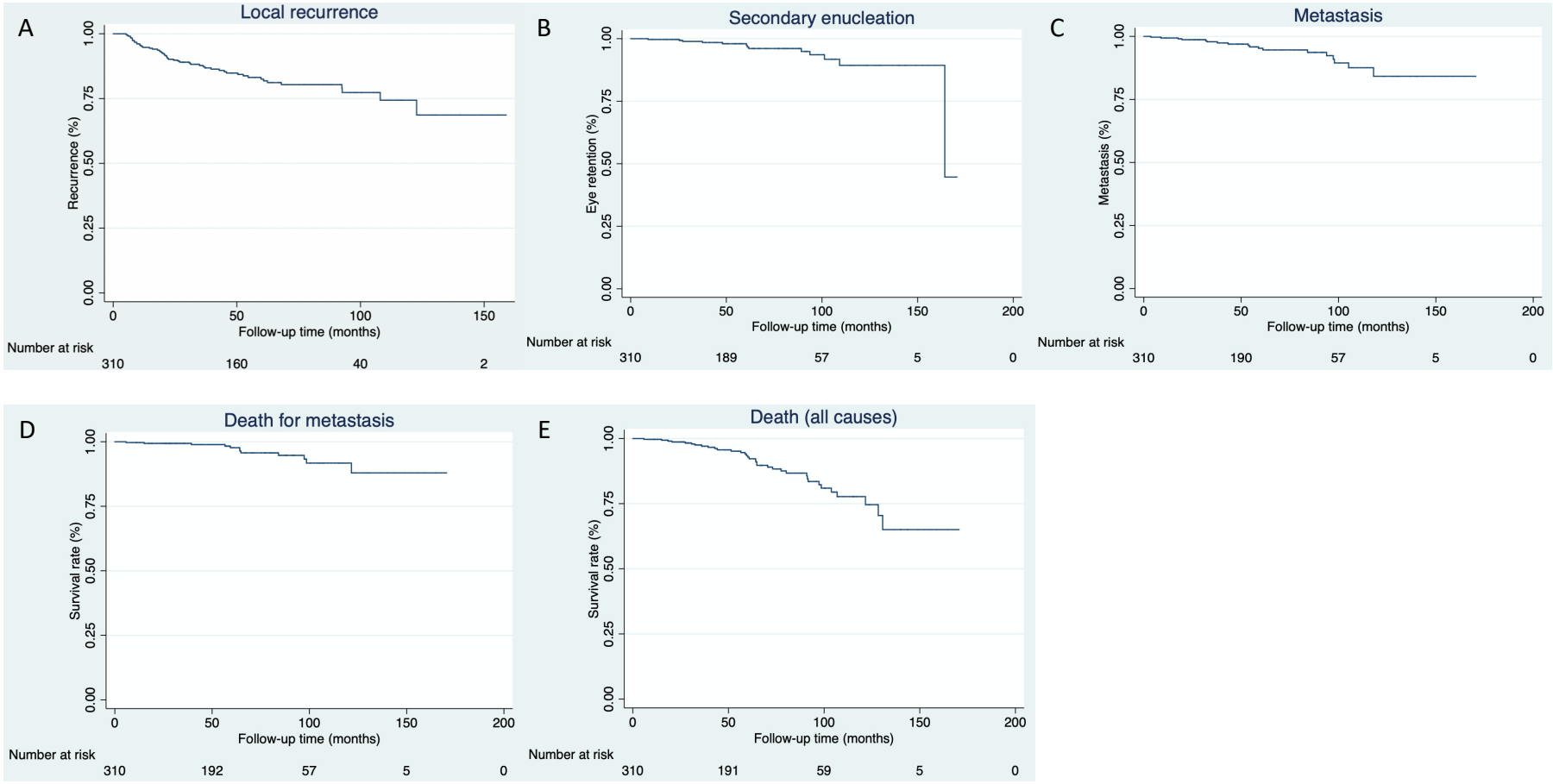

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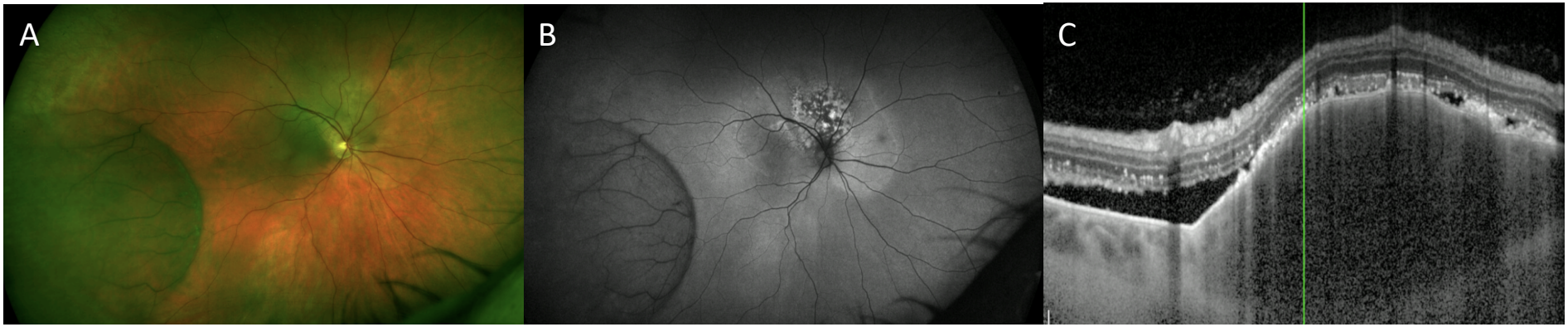

Table 4. Supplementary material. Clinical features associated with tumour recurrence and secondary enucleation after Ru-106 plaque brachytherapy for patients with small choroidal melanoma (n=310). Bold values indicate statistical significance.

	Univariable analysis		**Multivariable analysis**	
Tumour relapse	**Hazard ratio (95% CI)**	**P value**	**Hazard ratio (95% CI)**	**P value**
Male gender	0.5 (0.28-0.92)	0.025	0.78 (0.37-1.64)	0.51
Age	1.04 (1.01-1.06)	0.003	1.01 (0.98-1.05)	0.36
Peripheral tumour location	0.4 (0.21-0.95)	0.036	1.63 (0.47-5.65)	0.44
Juxtapapillary tumour location	2.58 (1.46-4.54)	0.001	0.25 (0.08-0.8)	**0.016**
Subretinal fluid	8.7 (1.2-63.2)	0.032	2.6 (0.3-22.6)	0.4
Orange pigment	5.67 (1.75-18.37)	0.004	2.78 (0.6-13.8)	0.2
Distance to fovea	0.85 (0.76-0.96)	0.010	1.18 (0.9-1.5)	0.2
Distance to disc	0.66 (0.56-0.78)	<0.001	0.58 (0.41-0.82)	**0.002**
15 mm plaque	3.98 (1.45-10.92)	0.007	-	>0.5
20 mm plaque	4.14 (1.47-11.61)	0.007	7844436 (1757361-3.50e+07)	**<0.001**
Final tumour thickness, mm	3.08 (2.26-4.21)	<0.001	3.4 (2.26-5.12)	**<0.001**
Second cancer	2.41 (1.18-4.93)	0.016	0.76 (0.26-2.23)	0.62
	Univariable analysis		**Multivariable analysis**	
Secondary enucleation	**Hazard ratio (95% CI)**	**P value**	**Hazard ratio (95% CI)**	**P value**
Juxta-papillary location	3.27 (1.08-9.91)	0.036	1.68 (0.27-10.53)	0.58
Baseline VA	2.8 (1.04-7.51)	0.041	4.13 (1.09-15.74)	**0.037**
Distance to fovea	0.70 (0.51-0.96)	0.029	0.61 (0.40-0.91)	**0.016**

Distance to disc	0.59 (0.41-0.85)	0.004	0.97 (0.52-1.82)	0.93
TTT	4.07 (1.29-12.84)	0.017	0.5 (0.1-2.48)	0.40
Second cancer	4.97 (1.43-17.3)	0.012	9.73 (1.94-48.75)	**0.006**

Table 5. Supplementary material. Clinical features associated with metastatic disease and death after Ru-106 plaque brachytherapy for patients with small choroidal melanoma (n=310). LBD: largest basal diameter. Values in bold indicate statistical significance.

	No (%)		**Univariable analysis**		**Multivariable analysis**	
	Metastases (n=18)	**No metastases** (n=292)	**Hazard ratio (95% CI)**	**P value**	**Hazard ratio (95% CI)**	**P value**
Collar-stud aspect	1 (5.6)	2 (0.7)	30.65 (3.37-278.79)	0.002	12.17 (0.51-288.48)	0.122
Initial tumour thickness, mm mean (SD) median (range)	 2.1 (0.4) 2.3 (1.1-2.5)	 1.9 (0.4) 2 (0.4-2.5)	3.95 (1.02-15.31)	0.047	0.76 (0.16-3.63)	0.736
Final tumour thickness, mm mean (SD) median (range)	 1.4 (1) 1.2 (0.5-5.1)	 1.2 (0.5) 1.1 (0-2.5)	2.41 (1.4-4.15)	0.002	0.96 (0.53-1.73)	0.889
Exudative retinal detachment	4 (22)	24 (8.2)	4.19 (1.3-13.51)	0.016	19.15 (3.31-110.65)	**0.001**
Tumour recurrence	4 (22)	48 (16)	1.13 (0.39-3.28)	0.83	-	-
	Death (n=35)	**No death** (n=275)				
Male sex	27 (77)	133 (48)	0.33 (0.15-0.72)	0.006	0.46 (0.2-1.06)	0.068
Age, mean (SD), years	69.9 (9.4)	59.5 (15)	1.09 (1.05-1.13)	<0.001	1.08 (1.04-1.13)	**<0.001**
Collar-stud aspect	1 (2.9)	2 (0.7)	13.8 (1.75-108.6)	0.013	4.92 (0.5-48.67)	0.17
LBD > 5 mm	29 (83)	193 (70)	2.54 (1.05-6.13)	0.038	1.29 (0.44-3.79)	0.64
Final tumour thickness, mm mean (SD) median (range)	 1.5 (0.8) 1.5 (0.8-2.5)	 1.2 (0.5) 1.1 (0-2.4)	2.54 (1.76-3.67)	<0.001	1.92 (1.28-2.87)	**0.001**
Metastasis	12 (34)	6 (2.2)	9.81 (4.87-19.75)	<0.001	8.34 (3.8-18.32)	**<0.001**