

1 **TITLE PAGE**

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

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26 **SYNOPSIS**

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

29

30 **SHORT TITLE**

31 Local control and survival in patients with small choroidal melanoma.

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33

34 **ABSTRACT**

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

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

40 **Results:** the final cohort included 310 eyes and tumour recurrence was observed in 52 (17%) eyes.
41 Ocular retention rate was 96%. Metastatic disease and tumour-related death occurred in 18 (5.8%)
42 and 12 (3.9%) patients, respectively. Metastases were diagnosed after a median of 54 (54 \pm 35; range
43 3.6-118) months from initial treatment. Kaplan-Meier estimates for tumour recurrence, melanoma-
44 related metastases and survival were 17% (95% CI, 13.3%-22.9%), 4.8% (95% CI, 2.6%-8.5%) and
45 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%)
46 and 92% (95% CI, 84.5%-95.7%) at 10 years, respectively. On multivariable analysis factors predictive
47 for tumour recurrence included juxtapapillary location, larger plaque and final tumour thickness,
48 and for metastasis exudative retinal detachment.

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

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53 **KEY WORDS**

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

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58 **What is already known on this topic**

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

62

63 **What this study adds**

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

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69 **How this study might affect research, practice or policy**

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

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83 **INTRODUCTION**

84 Choroidal melanoma (CM) is the most common primary intraocular cancer of adulthood with an
85 estimated incidence of 6-7 cases/million people/year (1) and more than 50% risk of metastasis at
86 10 years from initial diagnosis in large melanomas with adverse genetic profile (2). Of CMs, 30% are
87 small (3, 4) and 11% of uveal melanomas with systemic metastases at the time of tumour diagnosis
88 are stage T1 of the American Joint Committee on Cancer classification (AJCC, 8th edition) (5, 6).

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

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

106

107 **METHODS**

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

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

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

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

136

137 **Exclusion criteria**

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

141

142 **Treatment protocol**

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

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

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

162

163 **Follow-up**

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

172

173 **Metastatic surveillance**

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

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

182

183 **Statistical analysis**

184 Statistical analysis was performed using Microsoft Excel (version 16.41) and Stata software (version
185 14.1 StataCorp LP, TX, USA). Data are presented as mean \pm standard deviation (SD) when normally
186 distributed, or as median (interquartile range (IQR) and range) when not. Hypothesis testing used
187 two-tailed statistics and a significance was defined by p value of ≤ 0.05 . Categorical variables were
188 analyzed with chi-square and Fisher's exact tests. Kaplan-Meier methods were calculated for time
189 to event and used to estimate the cumulative probability of tumour recurrence, secondary
190 enucleation, metastasis and death. Univariate analyses using the Cox proportional hazards model
191 were performed to identify factors predictive of tumour recurrence, enucleation, metastases and
192 death based on clinical features at presentation and treatment parameters. Subsequent
193 multivariate analysis was performed using the forward stepwise method for factors deemed
194 statistically significant at $p \leq 0.05$ in the univariate analysis, to determine which combination of
195 factors best related to the studied event. Hazard ratios (HRs) with 95% confidence intervals (CIs)
196 were calculated for each risk factor. Patients were censored if death did not occur by the time of
197 last follow-up or occurred as a result of another cause.

198

199 **RESULTS**

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

202 Three hundred and ten eyes from three hundred and ten patients with a diagnosis of small CM (298
 203 stage T1a, 2 stage T1c, 10 stage T2a) were included in the analysis, with mean age of 58±14 (median
 204 60; range 25-89) years and median follow-up (from date of treatment to date of last visit) of 57
 205 (mean 64±36; range 3.4-171) months. 296 (96%) patients were white and 160 (52%) were male. 44
 206 (14%) patients had a second cancer in addition to the CM, and 82 (27%) had family history of cancer.
 207 Tumour location was posterior pole for 145 tumours (47%), peripheral for 95 (30%), juxta-papillary
 208 for 61 (20%) and both posterior pole and periphery for 9 (3%). Patient demographics and baseline
 209 tumour characteristics are summarized in table 1. Visual acuity and treatment-related side effects
 210 from this cohort have been reported separately (submitted).

211 **Table 1.**

212

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

213

214 **Treatment**

215 All eyes were treated with Ru-106 plaque, the only radioisotope used in our centre. Plaque size was
216 12 mm in 5 eyes (1.6%), 15 mm in 43 eyes (14%) and 20 mm in 262 eyes (84%); plaque shape was
217 notched for 91 (29%) tumours and circular for the remaining cases. A radiation apex dose of 100 Gy
218 was given to 249 (80%) eyes. Median time between tumour diagnosis and treatment was 30 (range
219 3-310) days.

220

221 **Tumour recurrence**

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

224 **Table 2.**

225

	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:	
- 2 nd Plaque	4
- PBRT	14
- TTT	
o alone	19
o combined with 2 nd 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

226

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

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

234 **Table 3.**

235

Outcomes	N (%)	Kaplan-Meier estimates, no. of affected patients/no. of unaffected patients (%) [95%CI]					
		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]

236

237

238 Factors best predictive of tumour recurrence on multivariate analysis were final tumour thickness
239 (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,
240 p=0.002) and 20 mm plaque size (p<0.001) (table 4, supplementary material).

241

242 **Secondary enucleation**

243 In this study 13 (4.2%) eyes underwent enucleation due to tumour recurrence after a median of 61
244 (mean 68, range 9-164) months from primary treatment, resulting in an ocular retention rate of
245 96%.

246 Kaplan-Meier 5-year and 10-year secondary enucleation rates were 2% and 11%, respectively (table
247 3 and figure 1B), and the factors predictive of enucleation on multivariate analysis were baseline
248 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-
249 0.91, p=0.016) and history of second cancer (HR 9.73, 95% CI, 1.94-48.75, p=0.006) (table 4,
250 supplementary material).

251

252 **Metastasis and death**

253 Distant metastases developed in 18 (5.8%) patients, and were hepatic in 14, multi-organ (liver,
254 spleen, bone, lungs) in two, and extra-hepatic (kidney, bone marrow) in two. Among these, 4
255 patients had also a second cancer, of whom two breast cancer, one mandibular melanoma and one
256 prostate cancer, and 5 had developed tumour recurrence. No patients had systemic metastases
257 synchronous with the primary tumour diagnosis. The metastasis-free interval, defined as median
258 time between CM diagnosis and metastatic disease detection, was 54 (54±35; range 4-118) months.
259 At the time of the analysis 35 (11%) patients had died, of whom 16 (5.2%) of unknown causes, 12
260 (3.9%) of metastatic disease, 2 (0.6%) of metastases from another cancer (esophageal and renal

261 cancer) and 5 (1.6%) of other causes. The median survival from diagnosis of metastatic disease was
262 6.7 (9.6±7.5; 2.2-22) months. At the end of the study 6 patients were alive with metastases.
263 Considering all causes of death, the median survival from tumour diagnosis was 64 (66±33; 5.8-131)
264 months.
265 Kaplan-Meier estimates for distant metastases were 4.8% and 16% at 5 and 10 years, respectively,
266 and the 5-year and 10-year survival rates were 98% and 92%, respectively (table 3 and figure 1C-E).
267 Factors predictive of metastases on univariate analysis were collar-stud shape (HR 30.65, 95% CI,
268 3.37-278.79, p=0.002), baseline (HR 3.95, 95% CI, 1.02-15.31, p=0.047) and final tumour thickness
269 (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,
270 p=0.016), and on multivariate analysis exudative retinal detachment (HR 19.15, 95% CI, 3.31-110.65,
271 p=0.001). 22% of patients with metastasis had developed tumour recurrence. However, no
272 correlation between tumour recurrence and metastasis was observed (p=0.83) (table 5,
273 supplementary material).
274 Factors predictive of death reaching statistical significance on multivariate analysis were older age
275 (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)
276 and metastasis (HR 8.34, 95% CI, 3.8-18.32, p<0.001) (table 5, supplementary material).

277

278 **DISCUSSION**

279 Our study reports the rates of tumour recurrence, secondary enucleation, distant metastases and
280 melanoma-related death for a large cohort of CMs less than 2.5 mm in thickness treated with
281 primary Ru-106 plaque brachytherapy. Few previous studies with limited number of cases (13, 16,
282 17, 18, 19, 20, 21, 22, 23, 24) specifically focused on outcomes of brachytherapy for tumours of this
283 size category, of which only two addressed Ru-106 (22, 23).

284 In our study 17% of eyes, more frequently affected by posterior pole and juxta-papillary tumours,
285 developed tumour recurrence that was managed conservatively with TTT or additional radiotherapy
286 in most cases (13%). Tumour recurrence was correlated with final tumour thickness ($p<0.001$) and
287 larger plaque size ($p<0.001$). Final tumour thickness may be an indicator of recurrence. The only
288 prior study on Ru-106 outcomes in 60 eyes with small CM (22) found lower recurrence rates (9-13%
289 at 5 years and 13-15% at 10 years), however the included tumours were smaller as their LBD was
290 less than 10 mm, while 24% of eyes in our cohort had LBD greater than 9 mm. Damato et al (23) in
291 their study showed significantly lower recurrence rates (1% at 2 years, 2% at 5 years, 3% at 7 years)
292 with Ru-106 plaque brachytherapy for tumours having median thickness of 3.2 mm (126 tumours
293 less than 2.5 mm); however, it is worth mentioning some key dissimilarities: their cohort included
294 also tumours involving the ciliary body; some patients received adjuvant TTT or photocoagulation 6
295 months after plaque to prevent tumour recurrence; patients treated with notched plaques were
296 not included; all surgeries were performed by a single highly experienced surgeon, while in our
297 series surgeries were performed by several surgeons with heterogenous levels of experience.
298 Conversely, the Small Fatal Choroidal Melanoma Study (19) showed higher tumour recurrence rates
299 (26%), but included also tumours managed with other primary treatment modalities (PBRT, TTT)
300 that in half of cases were observed before treatment.

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

306

307 Secondary enucleation was necessary in 4.2% of eyes after failure of conservative salvage therapies.
308 Our Kaplan-Meier estimates for enucleation at 5 and 10 years were 2% and 11%, respectively. These
309 figures are in keeping with both the Small Fatal Choroidal Melanoma Study (19) where enucleation
310 was performed in 4.4% of cases, and with studies on I-125 where enucleation rates ranged between
311 0.7% at 3 years (16) and 4% at 5 years (17, 20). History of second cancer was correlated to secondary
312 enucleation and this suggests that genetic abnormalities might predispose to more aggressive local
313 tumour behaviour and development of multiple cancers.

314

315 Distant metastases developed in 5.8% of patients, most commonly affecting the liver. Our
316 metastatic rates at 5 and 10 years were 4.8% and 16% respectively, which are in line with the
317 previously reported 5-year risk of metastasis for CM of thickness <3 mm ranging from 4.5% (17) to
318 16% (19, 27). 22% of patients with metastasis had developed tumour recurrence which is a known
319 risk factor for metastatic disease (28). However, we did not observe a statistically significant
320 correlation between tumour recurrence and metastasis, although this could be related to the small
321 number of study eyes.

322 Theoretical models suggest that the smallest CMs able to metastasize are ≥ 1 mm in thickness and \geq
323 3 mm in LBD (8). The two smallest previously reported metastasizing CMs have thickness of 1.7 mm
324 (29) and LBD of 3 mm (19). In our cohort the smallest metastasizing CM of a patient alive at the time
325 of analysis had thickness of 1.1 mm and LBD of 4.9 mm (figure 2), while the smallest metastasizing
326 and deadly CM had thickness of 1.3 mm and LBD of 5.4 mm.

327 By the end of the study 3.9% of patients died of metastatic CM after a median survival from primary
328 tumour diagnosis of 64 months (5.3 years) and from metastasis detection of 6.7 months. Our
329 melanoma-specific mortality rate is in line with the previous studies where it ranges between 0% at
330 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

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

335

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

350

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

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

369 In conclusion, our study shows that Ru-106 brachytherapy for small CM achieves tumour control in
370 83% and eye retention rate in 96% of cases, and is associated with 4.8% and 16% melanoma-related
371 metastases and 2% and 8% melanoma-related death rates at 5 and 10 years, suggesting that small
372 tumours can be lethal. The smallest metastasizing CM in this study had thickness of 1.1 mm and LBD
373 of 4.9 mm. Our treatment outcome data will act as a benchmark for future studies, especially in new
374 modalities of treatment, and support clinicians when counselling their patients.

375

376 TABLES

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

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

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

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

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

390
391 **FIGURES**

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

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

399
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403

404 **CONFLICT OF INTEREST**

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

406

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414

415 **CONTRIBUTORS**

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

419

420 **ETHICS STATEMENT**

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

423

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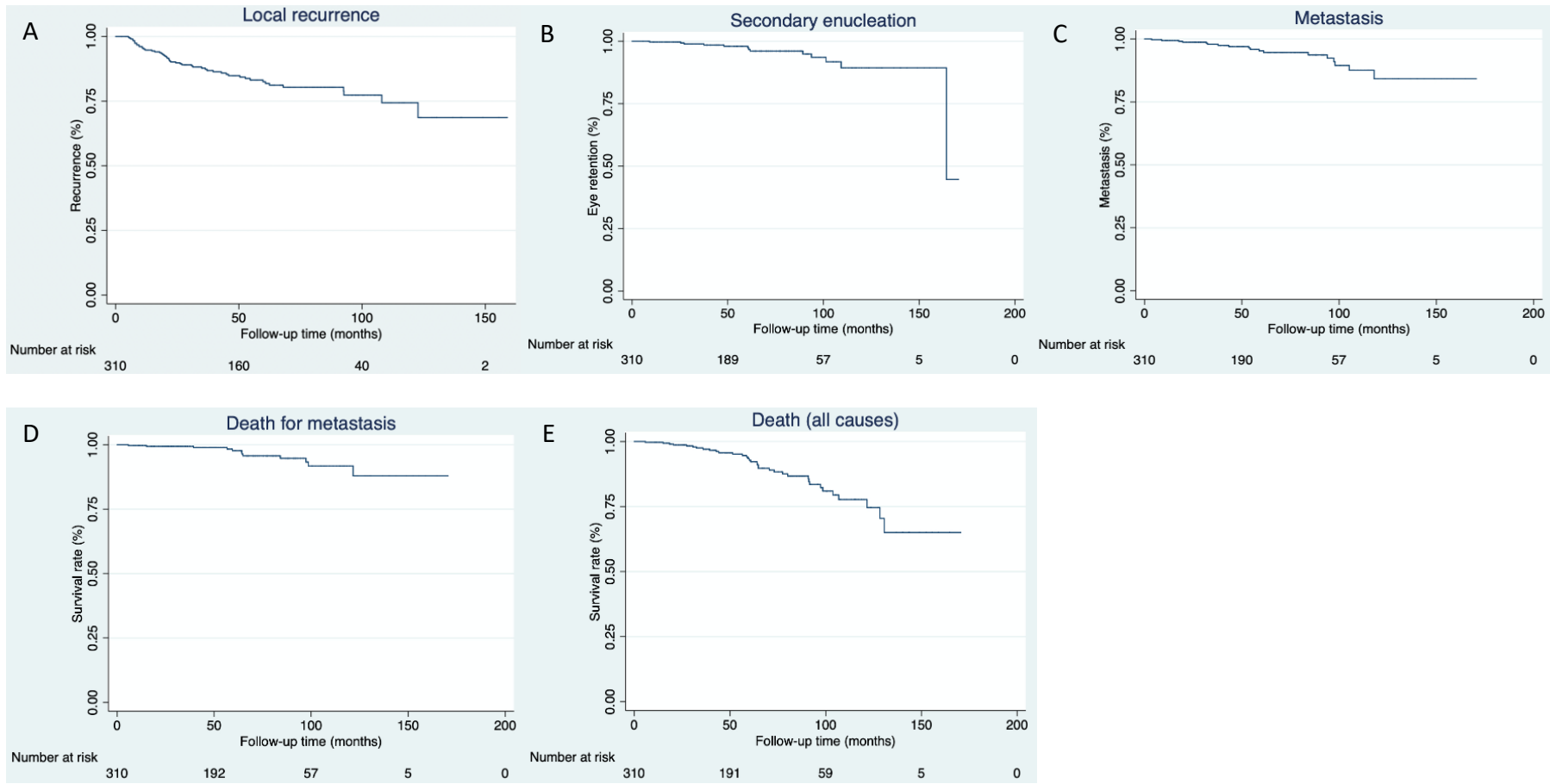
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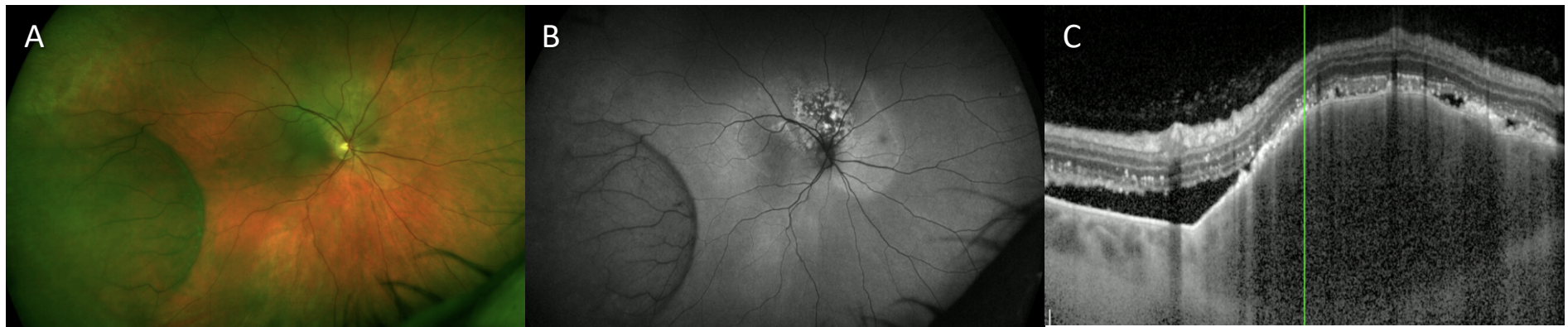
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Figure 1. Kaplan-Meier estimation of tumour recurrence (A), secondary enucleation (B), metastasis (C) and survival (D, E).



517

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 a thickness of 1.1 mm and a largest basal diameter of 4.9 mm, orange pigment and subretinal fluid. Infero-temporal peripheral bullous retinoschisis.



518

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

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