



# Long-term outcomes after enucleation or plaque brachytherapy of choroidal melanomas touching the optic disc

Maria Fili<sup>1,2</sup>, Melvin Astrahan<sup>3</sup>, Gustav Stålhammar<sup>1,2,\*</sup>

<sup>1</sup>Ophthalmic Pathology and Oncology Service, St. Erik Eye Hospital, Stockholm, Sweden

<sup>2</sup>Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden

<sup>3</sup>Department of Radiation Oncology, Keck School of Medicine, University of Southern California, Los Angeles, CA

## ABSTRACT

**PURPOSE:** To investigate local and systemic outcomes after enucleation, brachytherapy with ruthenium-106, iodine-125, notched and non-notched plaques and transpupillary thermotherapy (TTT) of choroidal melanomas touching the optic disc.

**METHODS AND MATERIALS:** All patients treated for choroidal melanoma touching the optic disc at St. Erik Eye Hospital, Stockholm, Sweden between 1984 and 2015 ( $n = 165$ ) were included. Retrospective clinicopathological data was collected and 3D dosimetry performed.

**RESULTS:** Ninety-five patients (58 %) had been treated with ruthenium-106 brachytherapy, 21 (13 %) with iodine-125 brachytherapy and 49 (30 %) with enucleation. Median follow-up was 12.3 years. In simulations, some tumor areas were underdosed with non-notched plaques. Fifty of 116 patients (43 %) underwent a secondary brachytherapy ( $n = 5$ ), enucleation ( $n = 29$ ) or TTT ( $n = 16$ ). In multivariate Cox Regressions, there were no significant differences in the risk for tumor progression or lack of regression between radioisotopes and notched and non-notched plaques. Adding TTT did not reduce the risk for a second treatment. The number of clock hours of circumpapillary tumor growth did not correlate to the risk for treatment failure or mortality. There were no significant differences in melanoma-related mortality for any treatment including enucleation. Kaplan-Meier disease-specific survival was 77 % at 5 years, 72 % at 10 years and 67 % at 20 years.

**CONCLUSION:** Plaque brachytherapy of choroidal melanomas touching the optic disc entails a two to threefold increased risk for treatment failure. This risk is similar between radioisotopes, notched and non-notched plaque designs and if TTT is used or not. The high rate of treatment failure does not lead to increased mortality. © 2021 The Authors. Published by Elsevier Inc. on behalf of American Brachytherapy Society. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>)

## Keywords:

Uveal melanoma; Brachytherapy; Enucleation; Transpupillary thermotherapy; Juxtapapillary; Dosimetry

## Introduction

At diagnosis, most patients with choroidal melanoma have medium sized tumors that can be safely treated with

eye-preserving plaque brachytherapy (1,2). Eye plaques are commonly shaped as concave discs that are temporarily sutured to the sclera overlying the tumor. Their inner surface contains seeds or foils of radioisotopes such as iodine-125, ruthenium-106 or Palladium-103 and their outer surface is commonly shielded by a precious metal such as silver or gold (3–5).

In the ageing but still very relevant Collaborative Ocular Melanoma Study, local treatment failure after plaque brachytherapy, defined as intraocular tumor growth, recurrence or extraocular extension, was observed in 10 % of patients (6,1). Thirteen percent of patients had undergone post brachytherapy (secondary) enucleation. Similar rates of secondary enucleation have been observed in two of

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**Abbreviations:** AJCC, American Joint Committee on Cancer; AUC, Area under the curve; COMS, Collaborative Ocular Melanoma Study; Gy, Gray; HR, Hazard ratio; PBRT, Proton beam radiation therapy; PDT, Photodynamic therapy; ROC, Receiver operating characteristics; SD, Standard deviation; TTT, Transpupillary thermotherapy.

\* Corresponding author. G. Stålhammar, Department of Clinical Neuroscience, St. Erik Eye Hospital, Karolinska Institutet, Eugeniavägen 12, Stockholm 17164, Sweden. Tel.: 0046 8 672 30 00; fax: 0046 8 672 33 75.

E-mail address: [gustav.stalhammar@ki.se](mailto:gustav.stalhammar@ki.se) (G. Stålhammar).

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our previous studies of 962 and 571 patients with long follow-up, respectively (7,8).

Uveal melanomas originating in the choroid close to the optic nerve (juxtapapillary) pose a special challenge to brachytherapy, as the nerve sheath may make it difficult to center the plaque above the tumor (9). In turn, this may lead to less than tumoricidal radioactive doses in tumor areas not fully covered by the plaque (10). In a large cohort of juxtapapillary choroidal melanomas, the 10-year rate of tumor recurrence and secondary enucleation was 21% and 26 %, respectively, twice the overall rate (11,12). These tumors may therefore require enucleation of the eye, even if the tumor dimensions would have allowed for plaque brachytherapy. Other approaches include using plaques that have an indent or notch that allow for placement around parts of the optic nerve sheath, or placing a circular plaque decentralized (eccentric) with or without addition of transpupillary thermotherapy (TTT) of tumor areas not covered by the plaque (13,14). A previous study with short follow-up achieved 100 % local control rate after brachytherapy with slotted iodine-125 plaques (15). TTT utilizes diode laser to raise the temperature within the tumor, leading to necrosis (13). Intravenous injection of a photosensitizing agent and tumor irradiation with infrared laser (photodynamic therapy, PDT) has also been evaluated (16). However, if used alone, both PDT and TTT is associated with increased risk for treatment failure (17,16).

In this study, we investigate the long-term results of ruthenium-106 brachytherapy and iodine-125 brachytherapy, of different types of notched and non-notched plaques as well as of enucleation. Local treatment success is compared in terms of lack of tumor regression and tumor progression after treatment, risk for secondary brachytherapy, enucleation or additional TTT. Radiation side effects are compared in terms of radiation retinopathy, neuropathy, neovascularization, bleeding and increased pressure. Last, we examine the risk for disease-specific mortality after the different treatment modalities.

## Materials and methods

This study was approved by the regional ethical review board in Stockholm (reference number 2016/247-31/4; and amendment 2019-03485 from the Swedish Ethical Review Authority) and adhered to the tenets of the Declaration of Helsinki.

All patients who had been treated for choroidal melanoma touching the optic disc at St. Erik Eye Hospital through December 31, 2015 were considered for the study ( $n=200$ ). Patients treated at a later date were not considered, to allow for a minimum of 5 years of follow-up. The first patient treated for a choroidal melanoma touching the optic disc in our treatment records was treated on August 8, 1984.

Of these 200 patients, 35 were excluded before further analysis: Fifteen because their tumor was found to

not actually touch the optic disc but leave a  $>0$  mm margin upon review of their fundus photographs. Ten because their actual treatment time deviated  $>10$  % from the planned treatment time, with resulting suboptimal radioactive doses. Seven because the type of applicator used (notched, non-notched, small diameter, large diameter etc.) was not specified. Two because their prescribed dose the tumor apex ( $+1$  mm for scleral thickness) was less than 70 Gray (Gy). One because she had a congenital visual field defect before treatment and therefore received an intentionally low prescribed dose of 16 Gy to the tumor apex. After these exclusions, 165 patients remained in the study.

Retrospective clinicopathological data including cause of death was retrieved from digitalized clinical records and from our digital Brachytherapy of Uveal Melanoma directory. Tumors that were deemed unsuitable for plaque brachytherapy were typically enucleated within 1–3 weeks from diagnosis. In most cases, this decision was motivated by an assessment that proper positioning of the plaque would not be possible, or because the tumor was  $>10$  mm thick and/or had a diameter of  $>16$  mm. However, there is a clear overlap in tumor sizes treated with plaque brachytherapy and enucleation due to the lack of consensus on the treatment of choice for choroidal melanoma touching the optic disc. Our protocol for ruthenium-106 brachytherapy allows for a maximum scleral dose of 1 500 Gy, elevated from 1 000 Gy in year 1999 following a report on radioactive tolerance of the sclera (18). This means that 100 Gy at the tumor apex  $+1$  mm can be prescribed for tumors with a thickness of up to approximately 7 mm. For iodine-125, 100 Gy was generally prescribed until 2003, after which it was lowered to 80 Gy due to concern for radiation damage to surrounding tissues. Ruthenium-106 plaques used for the included tumors were of the CCA (15.3 mm, circular), CCB (20.2 mm, circular), CIB (diameter 20.2 mm, semilunar) or COB (19.8 mm, circular with notch for optic nerve sheath) designs (Eckert & Ziegler BEBIG GmbH, Berlin, Germany). Iodine-125 plaques were custom-made by a goldsmith in 18-carat gold alloy to replicate the design of the ruthenium CCB, with a diameter of 20 mm, inner height of 5 mm and a thickness of 0.5 mm. The iodine seed model used with the plaque is the IsoSeed I25.S16 (Eckert & Ziegler BEBIG GmbH, Berlin, Germany). Plaque designs were not changed during the study period. As a safety margin of 2 mm is required around the tumor lateral margins, tumors up to 16 mm in diameter can be treated with plaque brachytherapy (20 mm minus 2 mm on each side of the tumor). No planning or calculation of radioactive dose at the tumor margins was conducted. Dosimetric aspects of the different types of plaques and radioisotopes have been published previously (19,20,4,5,10). Source specification data from the manufacturer of both radioisotopes were verified by medical physicists at the Karolinska University Hospital, Stockholm. At the discretion of the responsible ocular

oncologist, TTT could be added in cases in which it was suspected that optimal positioning of the plaque in relation to the tumor could not be obtained. Generally, TTT was given in the same session as the brachytherapy plaque was placed. All the relevant tumor areas were illuminated until they turned pale (typically 5–10 min), with a spot size of 2 mm and an energy setting of 500–600 mW.

After treatment, regular follow-up was scheduled at 1, 3, 6, and 12 months and then annually or semi-annually. At each visit, best-corrected visual acuity, intraocular pressure, biomicroscopy, ultrasonography with standardized A- and B-scan and fundus photographs were examined. When tumor regression was deemed insufficient or there was tumor progression  $\geq 6$  months after brachytherapy, a second treatment with TTT or plaque brachytherapy was considered. In cases of clear tumor progression where TTT or plaque brachytherapy was deemed insufficient, or if repeated TTT or brachytherapy already had been given without success, the eye was secondary enucleated. Semi-annual screening for liver metastases by ultrasonography or computed tomography was performed as metastatic screening for 5 years after choroidal melanoma diagnosis.

#### Dose simulations

Treatment plans and 3D dosimetry for the 3 most commonly used plaques (ruthenium-106 COB, ruthenium-106 CCB and iodine-125 CCB) were generated with Plaque Simulator version 6 (Eye Physics, LLC, Los Alamitos, CA, USA). A tumor with the same thickness and diameter as the mean in our cohort (5 and 10 mm, respectively), 5 clock hours of circumpapillary tumor growth and a nerve sheath diameter of 5 mm was assumed, and prescribed doses to the tumor apex of 100 Gy for ruthenium-106 and 80 Gy for iodine-125. Cumulative dose areas and doses to the tumor base, a 2 mm safety margin, optic disc, optic nerve, healthy retina and anterior segment including lens, ciliary body, iris and anterior chamber angle were compared. Each plane was modeled as a portion of a spherical shell and not flat surfaces.

#### Statistical analysis

Differences with a  $p < 0.05$  were considered significant, all  $p$ -values being two-sided. The deviation of continuous variables from normal distribution was not statistically significant when evaluated by the Shapiro-Wilk test ( $p > 0.05$ ). For comparisons of the distribution of continuous variables across two and more than two groups, we therefore used Student's  $t$  test and one-way ANOVA, respectively. For comparisons of categorical variables, two-by-two tables and Fisher's exact or chi-square tests were used. The sensitivity and specificity of the number of clock hours of circumpapillary tumor growth as a local and systemic prognostic marker was examined with receiver operating characteristics. The risk for a second brachytherapy,

secondary enucleation, additional TTT, tumor progression, lack of tumor regression and radiation-induced side effects were calculated with univariate and multivariate logistic regression. The hazard ratios (HR) for melanoma-related mortality with different treatment modalities and plaque designs were calculated with multivariate Cox Regression, adjusted for tumor size. To test whether our survival data met the proportional hazard assumption, we built a Cox regression model with a time dependent versus a time independent treatment variable (treatment type: Enucleation or plaque brachytherapy with ruthenium-106 or iodine-125). Melanoma-related mortality was defined as death from metastatic choroidal melanoma. All statistical analyses were performed using SPSS statistics version 25 (IBM, Armonk, NY, USA).

## Results

### Descriptive statistics

Of the 165 included patients, 79 (48 %) were female and 86 (52 %) were male. Their mean age at choroidal melanoma diagnosis was 61 years (SD 15). No tumor infiltrated the ciliary body and only 1 patient had extrascleral tumor growth. The average number of clock hours of circumpapillary tumor growth was 4 (SD 2, range 1–10). Ninety-five patients (58 %) had been treated with ruthenium-106 brachytherapy, 21 (13 %) with iodine-125 brachytherapy and 49 (30 %) with enucleation. Of the 95 patients that had been treated with ruthenium-106, 19 (20 %) had been treated with the small diameter CIA plaque design, 30 (32 %) with notched COB plaques and the remaining 46 (48 %) with CCB plaques. Of the 21 patients treated with iodine-125, all had been treated with CCB plaques (Fig. 1). Our data met the proportional hazard assumption ( $p = 0.11$ ). Eighty-nine patients (54 %) were deceased before the end of follow-up. Of these 89, 43 (48 %) had deceased from metastatic choroidal melanoma. TTT was added to the primary brachytherapy for 49 of 116 patients (42 %). The median follow-up for the 76 survivors was 12.3 years (SD 7.4, Table 1).

### Dose simulations

In simulations of treatment of identical 5 mm thick choroidal melanomas touching the optic disc, the cumulative retinal plane dose area was highest with ruthenium-106 COB, with no portion of the tumor base or 2 mm safety margin receiving less than 60 Gy. Treatment with ruthenium-106 CCB led to slightly lower doses, with areas of the 2 mm safety margin receiving less than 30 Gy and the prescribed dose of 100 Gy only delivered to 70% to 80 % of the targeted tumor base and safety margin. Even lower doses were delivered to the tumor base and safety margin with iodine-125 CCB.

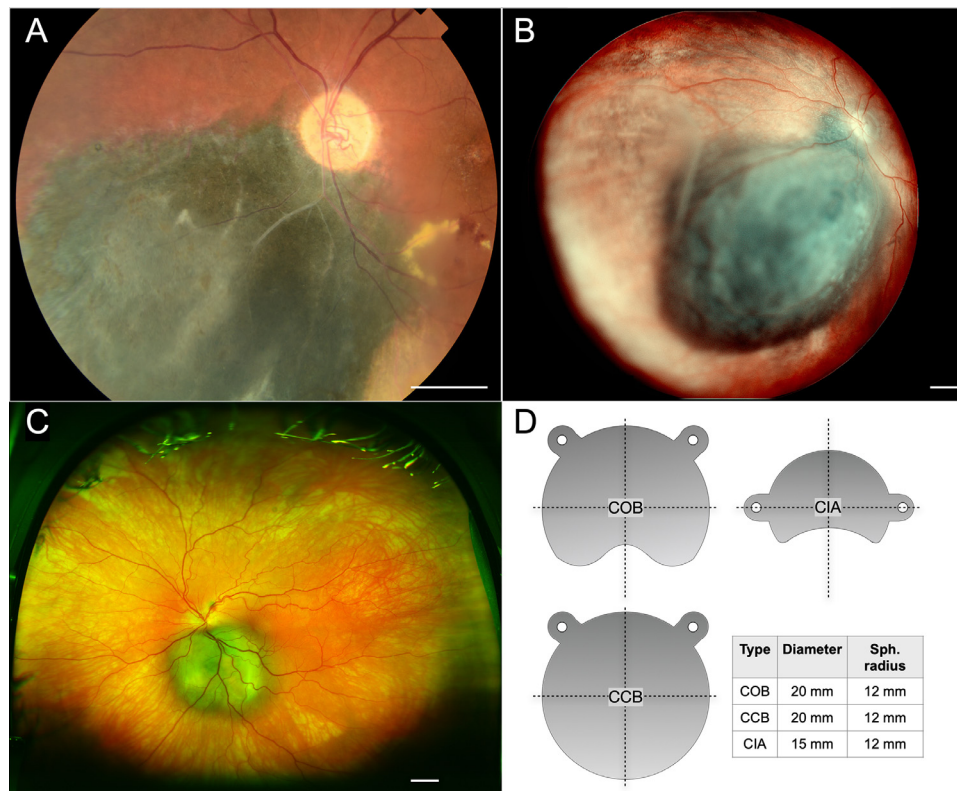


Fig. 1. Examples of the visual appearance of choroidal melanoma touching the optic disc and brachytherapy plaques. (a and b) Fundus photographs showing darkly pigmented tumors growing circumpapillary in 4 and 5 clock hours, respectively. The former is quite flat whereas the latter is protruding. (c) Appearance in wide field fundus photography (Optos, Inc, Dunfermline, UK). (d) Plaque size measurements and illustration of the basic shape differences between notched COB plaques (top) and circular CCB plaques (bottom). Sph., spherical. Scale bars 1.5 mm.

Doses to the optic disc were highest with ruthenium-106 COB, with 100 % of the area receiving  $>80$  Gy, and the optic nerve sheath to a depth of 1.5 mm below the disc surface receiving  $>45$  Gy. This was about twice the dose generated by ruthenium-106 CCB and iodine-125 CCB at approximately 40 Gy.

With the ruthenium-106 CCB plaque, 13 % of the healthy retina outside the tumor received  $>400$  Gy versus only 60 % of the tumor base plus safety margin, meaning that a larger area of healthy retina received  $>400$  Gy than the tumor itself ( $131 \text{ mm}^2$  retina vs.  $101 \text{ mm}^2$  tumor). With the ruthenium-106 COB plaque, 4 % of the healthy retina outside the tumor received  $>400$  Gy versus 79 % of the tumor base ( $40 \text{ mm}^2$  retina vs.  $133 \text{ mm}^2$  tumor). With the iodine-125 CCB plaque, no portion of healthy retina or tumor base received  $>400$  Gy.

Doses to the lens, ciliary body, iris and anterior chamber angle were higher with iodine-125 CCB than with ruthenium-106 CCB, which were higher than with ruthenium-106 COB (Fig. 2).

#### Treatment failure

Twenty-seven patients (23 %) suffered from tumor progression or lack of regression after brachytherapy. Another

19 patients (16 %) suffered from radiation-induced side effects including radiation retinopathy, radiation neuropathy, retinal or iris neovascularization, bleeding, increased ocular pressure or great loss of vision. Fifty of 116 patients (43 %) had to undergo either a second brachytherapy ( $n=5$ , 4 %), secondary enucleation ( $n=29$ , 25 %) or an additional TTT ( $n=16$ , 14 %). One patient first underwent a re-treatment with iodine-125 plaque brachytherapy and then enucleation.

#### Differences in tumor size and in secondary treatment

Iodine-125 brachytherapy had been used for tumors with significantly larger diameter and thickness than tumors in eyes that had been enucleated (one-way ANOVA  $p < 0.001$ ). In turn, tumors in eyes that had been enucleated were significantly larger than tumors that had been treated with ruthenium-106 ( $p < 0.001$ , Table 2).

Including all plaque designs, TTT was added to significantly more primary ruthenium-106 than iodine-125 treatments (Fisher's exact  $p=0.006$ ). After the primary plaque brachytherapy with ruthenium-106 versus iodine-125, there were however no significant differences in the number of secondary plaque brachytherapies, secondary enucleations and/or in additional treatments with TTT (Table 3).



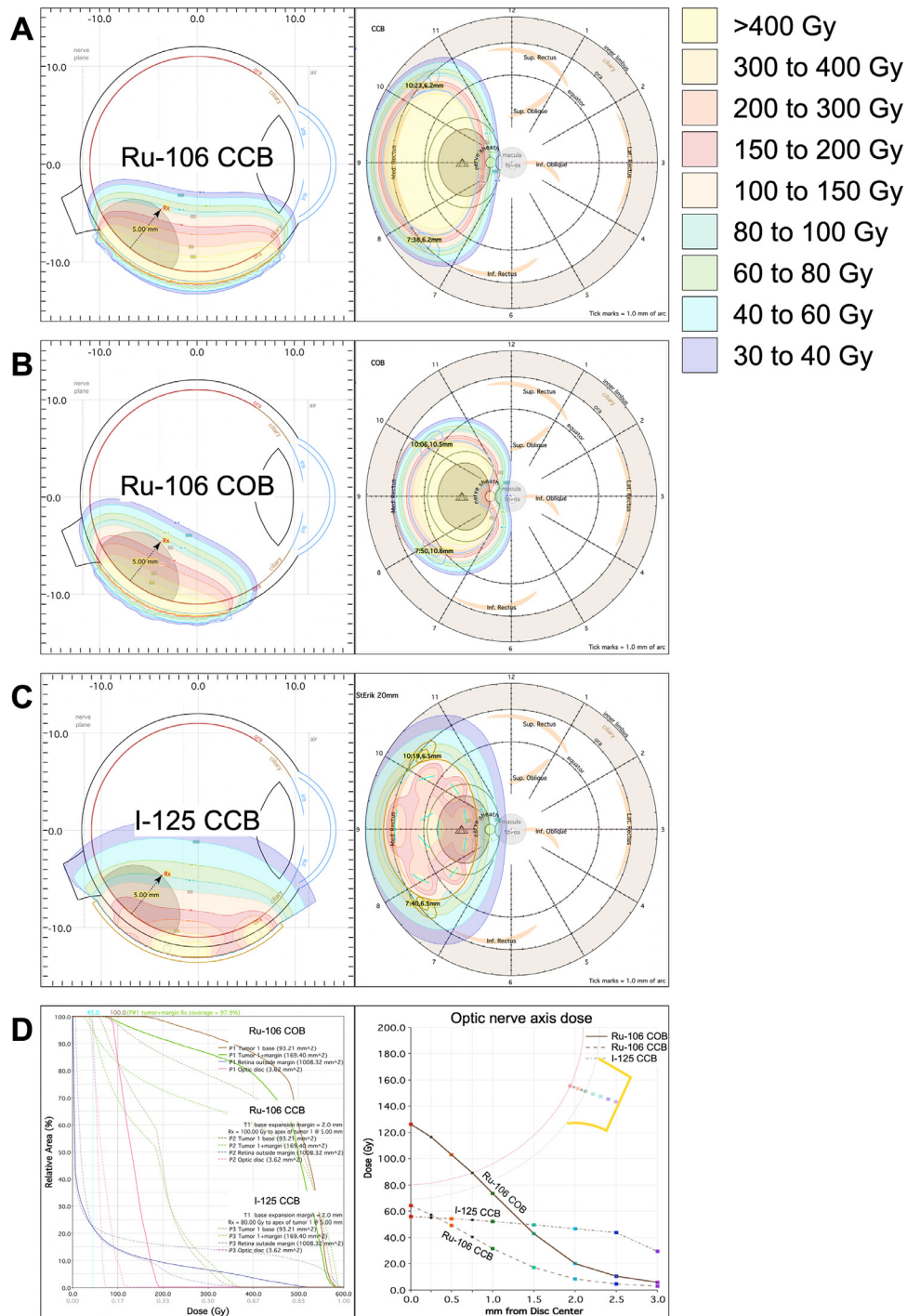


Fig. 2. Dose simulations in the treatment of a choroidal melanoma with a thickness of 5 mm and a diameter of 10 mm, with 5 clock hours of circumpapillary tumor growth. 100 Gy is prescribed to the tumor apex with ruthenium-106 CCB (a, Ru-106 CCB) and ruthenium-106 COB (b, Ru-106 COB). 80 Gy is prescribed with iodine-125 CCB (c, I-125 CCB). (d) In comparisons of cumulative retinal plane dose area, ruthenium-106 COB generated the highest doses in all areas of the tumor base, with no portion or 2 mm safety margin receiving less than 70 Gy. Treatment with ruthenium-106 CCB led to slightly lower doses, with areas of the 2 mm safety margin receiving less than 30 Gy. The lowest doses to the tumor base and safety margin were generated with iodine-125 CCB. Similarly, ruthenium-106 COB led to higher doses in the first 1.5 mm of the optic nerve sheath (axial plane) than treatment with iodine-125 CCB, which in turn led to higher doses than ruthenium-106 CCB.

Table 1  
Demographics and clinical features of study patients and tumors.

n=	165
Treatment modality, n (%)	
Ruthenium-106	95 (58)
Iodine-125	21 (13)
Enucleation	49 (30)
Mean age at diagnosis, years (SD)	61 (15)
Sex, n (%)	
Female	79 (48)
Male	86 (52)
Mean tumor thickness, mm (SD)	5.0 (2.3)
Mean tumor diameter, mm (SD)	10.5 (3.2)
Primary tumor location, n (%)	
Choroid	165 (100)
Ciliary body	0 (0)
Iris	0 (0)
Extrasccleral growth	
No	164 (99)
Yes	1 (1)
Ciliary body or iris engagement, n (%)	
No	165 (100)
Yes	0 (0)
Mean clock hours of circumpapillary tumor growth, n (SD)	4 (2)
AJCC T-category, n (%)	
1a	60 (36)
1b–d	0 (0)
2a	68 (41)
2b–d	0 (0)
3a	17 (10)
3b	0 (0)
3c	1 (1)
3d	0 (0)
4a	19 (12)
4b–d	0 (0)
AJCC stage, n (%)	
I	60 (36)
IIA	68 (41)
IIB	17 (10)
IIIA	20 (12)
IIIB	0 (0)
IIIC	0 (0)
IV	0 (0)
Follow-up years, median (SD)	12.3 (7.4)

AJCC = American Joint Committee on Cancer.

Including only notched ruthenium-106 COB ( $n=30$ ) versus iodine-125 CCB ( $n=20$ ) plaques, the latter had been used for thicker tumors (Students  $t$  test  $p < 0.001$ ) whereas the former had been used for tumors with more

Table 2  
Mean tumor measurements at brachytherapy and primary enucleation.

	Treatment	Mean	SD	$p$
Tumor thickness, mm	Ruthenium	4.0	1.3	<0.001
	Iodine	8.2	1.5	
Tumor diameter, mm	Enucleation	5.9	2.7	<0.001
	Ruthenium	9.6	2.7	
	Iodine	11.6	2.9	
	Enucleation	11.9	3.5	

clock hours of circumpapillary tumor growth ( $p=0.018$ , Table 4).

However, in analysis of receiver operating characteristics, the number of clock hours of circumpapillary tumor growth had low sensitivity and specificity for the need for a secondary brachytherapy, secondary enucleation or additional TTT (Area under the curve, AUC 0.57,  $p=0.29$ ) as well as for melanoma-related mortality (AUC 0.40,  $p=0.19$ ). No threshold could be identified that reliably indicated outcome: Patients with tumors that grew more than 6 clock hours around the optic nerve head did not have higher risk for treatment failure or mortality than patients with fewer clock hours of circumpapillary growth (Fig. 3).

#### Logistic regression

In univariate binary logistic regression, tumor thickness (Exp(B) 0.7,  $p=0.024$ ), iodine-125 versus ruthenium-106 brachytherapy including all plaque designs (Exp(B) 0.1,  $p=0.028$ ) and iodine-125 CCB versus ruthenium-106 COB brachytherapy (Exp(B) 0.1,  $p=0.028$ ) were associated with *decreased* risk for tumor progression or lack of regression (Table 5A).

In multivariate regressions adjusting for tumor thickness, the significant associations disappeared (Table 5B and 5C).

In univariate binary logistic regression, TTT added to primary brachytherapy was associated with *decreased* risk for secondary brachytherapy, secondary enucleation or additional TTT (Exp(B) 0.4,  $p=0.012$ , Table 6A).

However, TTT added to primary brachytherapy did not retain its significant association when adjusting for tumor size and radioisotope used in multivariate regression (Table 6B and 6C).

Table 3  
Rates of secondary treatment after primary Iodine-125 versus primary Ruthenium-106 treatment.

	Iodine-125	Ruthenium-106	$p$
TTT at first brachytherapy, n	3 of 21	46 of 95	0.006
Secondary brachytherapy, n	0 of 21	5 of 95	0.58
Secondary enucleation, n	6 of 21	23 of 95	0.78
Additional TTT, n	1 of 21	15 of 95	0.30
Secondary brachytherapy, secondary enucleation or additional TTT, n	7 of 21	37 of 95	0.81

TTT = Transpupillary thermotherapy.

Table 4

Differences in tumour size and clock hours of circumpapillary tumour growth at treatment with Ruthenium-106 COB versus Iodine-125 CCB plaque designs.

	Treatment	N	Mean	SD	<i>p</i>
Tumor diameter, mm	Ruthenium COB	30	10.1	2.7	0.12
	Iodine CCB	20	11.4	2.9	
Tumor thickness, mm	Ruthenium COB	30	4.2	1.3	<0.001
	Iodine CCB	20	8.3	1.5	
Clock hours of circumpapillary growth	Ruthenium COB	30	5.1	2.0	0.018
	Iodine CCB	20	3.6	2.0	

Table 5

A) Univariate and B+C) multivariate binary logistic regressions of risk factors for tumour progression or lack of regression after plaque brachytherapy.

A

	B	S.E.	Wald	<i>p</i>	Exp(B)
Sex	-0.8	0.6	1.9	0.17	0.4
Age at diagnosis, per year	-0.004	0.02	0.04	0.85	1.0
Tumor diameter, per mm	-0.02	0.1	0.02	0.89	1.0
Tumor thickness, per mm	-0.4	0.2	5.1	0.024 <sup>a</sup>	0.7
Per clock hour of circumpapillary growth	0.2	0.2	1.2	0.27	1.2
TTT at first brachytherapy, yes vs. no	-0.1	0.6	0.02	0.89	0.9
Iodine vs. Ruthenium, all plaques	-2.5	1.1	4.8	0.028 <sup>a</sup>	0.1
Iodine CCB vs. Ruthenium COB	-2.8	1.3	4.8	0.028 <sup>a</sup>	0.1

	B	S.E.	Wald	<i>p</i>	Exp(B)
Tumor thickness, per mm	-0.2	0.2	0.7	0.41	0.8
Iodine vs. Ruthenium, all plaques	-1.7	1.4	1.5	0.23	0.2
Constant	3.2	1.3	6.3	0.012	25.0

	B	S.E.	Wald	<i>p</i>	Exp(B)
Tumor thickness, per mm	0.5	0.5	0.9	0.33	1.7
Iodine CCB vs. Ruthenium COB	-5.3	3.1	2.9	0.09	0.01
Constant	-0.9	2.2	0.2	0.67	0.4

<sup>a</sup> significant on a 0.05 level.

Table 6

A) Univariate and B+C) multivariate binary logistic regressions of risk factors for secondary brachytherapy, secondary enucleation or additional TTT after plaque brachytherapy.

A

	B	S.E.	Wald	<i>p</i>	Exp(B)
Sex	-0.1	0.4	0.1	0.71	0.9
Age at diagnosis, per year	-0.01	0.01	1.0	0.32	1.0
Tumor diameter, per mm	-0.1	0.1	1.5	0.23	1.0
Tumor thickness, per mm	-0.02	0.1	0.03	0.86	1.0
Per clock hour of circumpapillary growth	0.1	0.1	1.5	0.23	1.1
TTT at first brachytherapy, yes vs. no	-1.0	0.4	6.3	0.012 <sup>a</sup>	0.4
Iodine vs. Ruthenium, all plaques	-0.2	0.5	0.2	0.63	0.8
Iodine CCB vs. Ruthenium COB	-1.0	0.6	2.9	0.087	0.4

	B	S.E.	Wald	<i>p</i>	Exp(B)
Tumor thickness, per mm	-0.2	0.2	0.7	0.41	0.8
Iodine vs Ruthenium, all plaques	-1.7	1.4	1.5	0.23	0.2
Constant	3.2	1.3	6.3	0.012	25.0

	B	S.E.	Wald	<i>p</i>	Exp(B)
Tumor thickness, per mm	0.5	0.5	0.9	0.33	1.7
Iodine CCB vs. Ruthenium COB	-5.3	3.1	2.9	0.09	0.01
Constant	-0.9	2.2	0.2	0.67	0.4

<sup>b</sup> asignificant on a 0.05 level

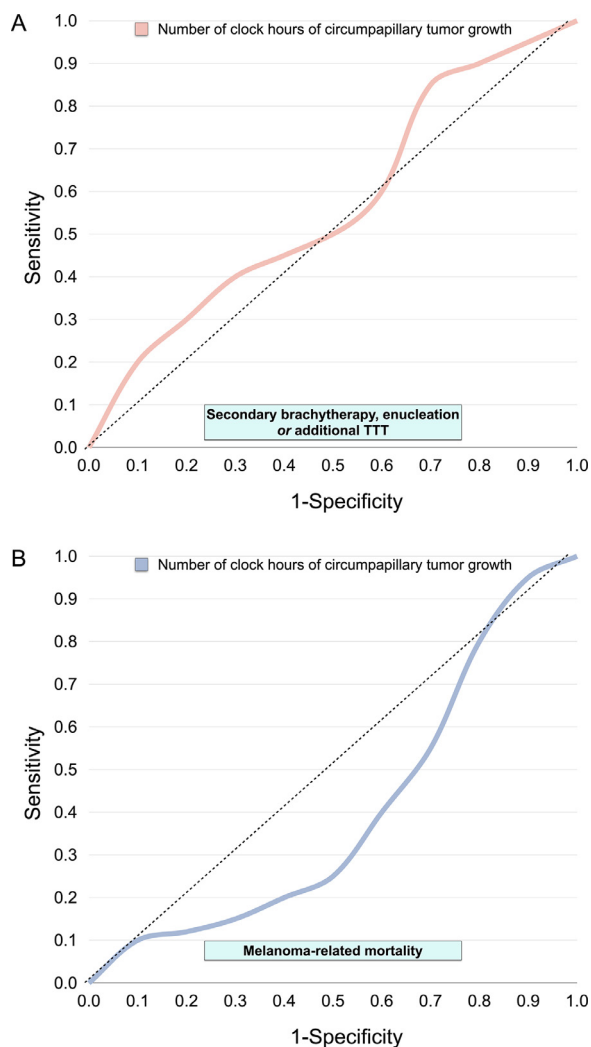


Fig. 3. Receiver operating characteristics for the sensitivity and specificity of the number of clock hours of circumpapillary growth for the risk of (a) secondary brachytherapy, secondary enucleation or additional TTT (AUC 0.57,  $p=0.29$ ), and (b) Melanoma-related mortality (AUC 0.40,  $p=0.19$ ).

Iodine-125 versus ruthenium-106 brachytherapy including all plaque designs (Exp(B) 10.7,  $p=0.036$ ) and iodine-125 CCB versus ruthenium-106 COB brachytherapy (Exp(B) 16.7,  $p=0.028$ ) were associated with greatly increased risk for radiation-induced side effects including radiation retinopathy, radiation neuropathy, retinal or iris neovascularization, bleeding, increased ocular pressure or great loss of vision (Table 7A).

But similarly, these associations disappeared when adjusting for tumor thickness (Table 7B and 7C).

### Survival

In univariate Cox regressions, age at diagnosis (Hazard ratio, HR 1.2 per increased decade,  $p=0.045$ , 95 % CI 1.0–1.5), tumor diameter (HR 1.2 per increased millimeter,  $p < 0.001$ , 95 % CI 1.1–1.3), and enucleation (HR

2.3,  $p=0.005$ , 95 % CI 1.3–4.3), were associated with melanoma-related mortality (Table 8A).

In multivariate regression, only tumor diameter retained its prognostic significance (Table 8B).

Kaplan-Meier disease-specific survival was 77 % at 5 years, 72 % at 10 years, 69 % at 15 years, and 67 % at 20 and 25 years after primary treatment (Fig. 4).

### Discussion

In this paper, we have compared local and systemic outcomes after treatment with plaque brachytherapy, TTT or enucleation of choroidal melanomas touching the optic disc. Several conclusions can be drawn. Among these, the most important is likely the fact that more than 2 in 5 patients (43 %) treated with primary brachytherapy had to undergo a secondary brachytherapy, secondary enucleation or an additional TTT. This is approximately two to threefold the overall rate (1,7,21). Our 25 % rate of secondary enucleation is almost identical to the 26 % 10-year rate in the large cohort of juxtapapillary melanomas examined by Sagoo *et al.* in 2014, even though our tumors were larger (thickness 3.5 vs. 5.0 mm) with longer follow-up (40 months vs. 12.3 years) (12). Nonetheless, Sagoo *et al.* concluded that “Plaque radiotherapy remains a suitable choice for the treatment of juxtapapillary melanoma with a high globe retention rate.” We are less pleased, and stress the need for clinicians and patients to be aware of the high risk of treatment failure when planning brachytherapy of a choroidal melanoma touching the optic disc. A higher proportion of these tumors should probably be enucleated, and there is room to improve our practices of dose and treatment planning.

In 2011, Lane *et al.* reported a 17 % secondary enucleation rate after proton beam radiation therapy (PBRT) of choroidal melanomas of similar mean size located within 1 disc diameter of the optic nerve (22). Furthermore, the 10-year local recurrence rate after PBRT was 6 %. This exact rate of local recurrences was repeated in a 2014 paper by Reichardt *et al.* after a mean of 23 months (23). No identical comparisons exist, but it is likely safe to say that this is considerably better than the 23 % rate of tumor progression or lack of regression after brachytherapy in our cohort, and the 21 % recurrence rate (no data on lack of regression) reported by Sagoo *et al.* (11). A higher risk of recurrence after ruthenium-106 brachytherapy versus iodine-125 brachytherapy and PBRT has been found in a previous retrospective non-randomized study (24). To the best of our knowledge however, no prospective randomized trial has been conducted comparing PBRT and plaque brachytherapy for melanoma in any part of the choroid, let alone for juxtapapillary tumors.

Further, we showed that there are no significant differences in the risk for tumor progression or lack of regression, in the need for a second treatment or in the risk for melanoma-related mortality between young and old pa-



Table 7

A) Univariate and B+C) multivariate binary logistic regressions of risk factors for radiation-induced side effects including radiation retinopathy, radiation neuropathy, retinal or iris neovascularisations, bleeding, increased intraocular pressure or great loss of vision after plaque brachytherapy.

A					
	B	S.E.	Wald	<i>p</i>	Exp(B)
Sex	0.7	0.6	1.2	0.27	2.0
Age at diagnosis, per year	-0.01	0.02	0.06	0.80	1.0
Tumor diameter, per mm	0.02	0.1	0.03	0.87	1.0
Tumor thickness, per mm	0.3	0.2	3.7	0.056	1.4
Per clock hour of circumpapillary growth	-0.2	0.2	1.3	0.26	0.8
TTT at first brachytherapy, yes vs. no	0.4	0.6	0.3	0.56	1.5
Iodine vs. Ruthenium, all plaques	2.4	1.1	4.4	0.036 <sup>a</sup>	10.7
Iodine CCB vs. Ruthenium COB	2.8	1.3	4.9	0.028 <sup>a</sup>	16.7
B					
	B	S.E.	Wald	<i>p</i>	Exp(B)
Tumor thickness, per mm	-0.2	0.2	0.7	0.41	0.8
Iodine vs. Ruthenium, all plaques	-1.7	1.4	1.5	0.23	0.2
Constant	3.2	1.3	6.3	0.012	25.0
C					
	B	S.E.	Wald	<i>p</i>	Exp(B)
Tumor thickness, per mm	-0.5	0.5	0.9	0.33	0.6
Iodine CCB vs. Ruthenium COB	5.3	3.1	2.9	0.086	201.4
Constant	0.9	2.2	0.2	0.67	2.5

<sup>a</sup> significant on a 0.05 level.

Table 8

A) Univariate and B) multivariate Cox regression analysis of risk factors for melanoma-related mortality after plaque brachytherapy and primary enucleation.

A							
	B	S.E.	Wald	<i>p</i>	Exp(B)	95 % CI, lower	95 % CI, upper
Sex	-0.5	0.3	2.1	0.15	0.6	0.3	1.2
Age at diagnosis, per year	0.2	0.01	4.2	0.039 <sup>a</sup>	1.0	1.0	1.0
Age at diagnosis, per decade	0.2	0.1	4.0	0.045 <sup>a</sup>	1.2	1.0	1.5
Tumor diameter, per mm	0.2	0.05	13.1	<0.001 <sup>a</sup>	1.2	1.1	1.3
Tumor thickness, per mm	0.1	0.06	1.6	0.21	1.1	1.0	1.2
Per clock hour of circumpapillary growth	-0.2	0.1	1.7	0.20	0.9	0.7	1.1
TTT at first brachytherapy, yes vs. no	-0.9	0.5	3.0	0.08	0.4	0.2	1.1
Second brachytherapy, secondary enucleation or additional TTT, yes vs. no	0.8	0.4	3.6	0.06	2.3	1.0	5.2
Iodine vs. Ruthenium, all plaques	-0.4	0.6	0.4	0.53	0.7	0.2	2.3
Iodine CCB vs. Ruthenium COB	-0.6	0.7	0.9	0.35	0.5	0.1	2.0
Enucleation vs. plaque brachytherapy	0.9	0.3	7.7	0.005 <sup>a</sup>	2.3	1.3	4.3
B							
	B	S.E.	Wald	<i>P</i>	Exp(B)	95 % CI, lower	95 % CI, upper
Age at diagnosis, per year	0.01	0.01	1.4	0.24	1.0	1.0	1.0
Tumor diameter, per mm	0.1	0.06	6.4	0.011 <sup>a</sup>	1.2	1.0	1.3
Tumor thickness, per mm	-0.01	0.07	0.01	0.94	1.0	0.9	1.1
Enucleation vs. plaque brachytherapy	0.6	0.3	3.2	0.075	1.8	0.9	3.4

<sup>c</sup> as significant on a 0.05 level

tients, men and women, ruthenium-106 and iodine-125 and notched and non-notched plaques— as long as we adjust for tumor size. Similarly, adding TTT to primary brachytherapy did not reduce the risk for a second treatment when adjusting for the tumor size and the used radioisotope. This

lack of benefit of TTT is noteworthy, considering that it may be associated with substantial visual loss and relatively high rates of treatment failure (13,25,26,17).

Quite surprisingly, the number of clock hours of circumpapillary growth was not associated with treatment failure

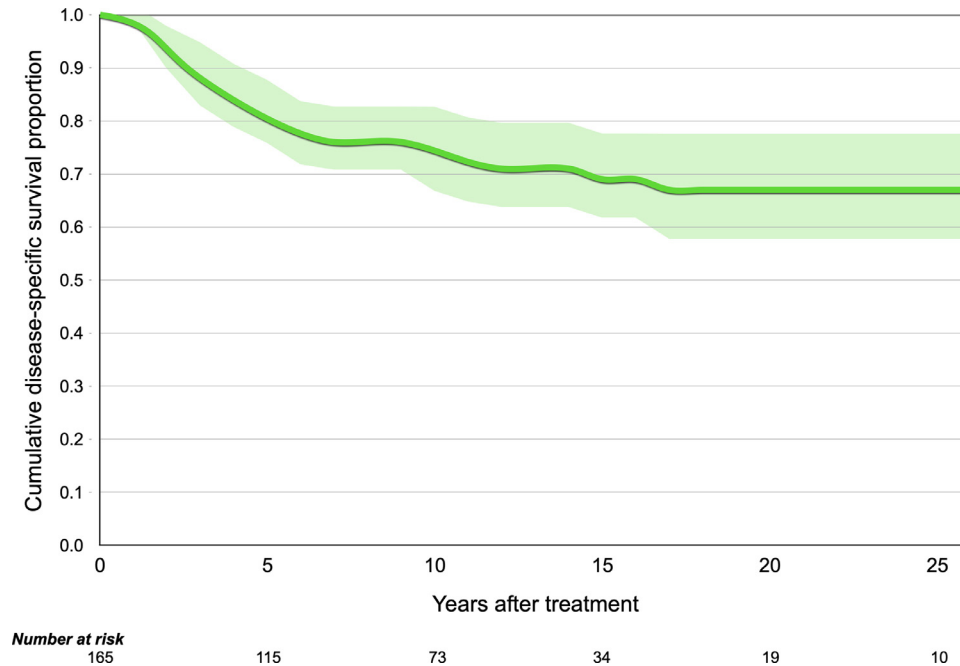


Fig. 4. Kaplan-Meier curve. Disease-specific survival for 165 choroidal melanomas touching the optic disc, treated with brachytherapy or enucleation.

or melanoma-related mortality, and iodine-125 brachytherapy did not correlate to radiation side-effects when adjusting for tumor size.

Despite the high rate of treatment failure, the melanoma-related mortality was similar to other cohorts of choroidal melanoma with similar mean size that were not selected for their vicinity to the optic nerve (27–29). This may support a notion that the documented association between local recurrence and poor survival is not caused by the recurrence in itself, but by a higher probability of recurrence for tumors that were more aggressive from the start (30).

Considering that iodine-125 has a less steep dose fall-off rate than ruthenium-106, a greater number of eyes with radiation side effects could have been expected regardless of tumor size. Similarly, the negative correlation between tumor thickness and tumor progression shown here is both surprising and paradoxical. We interpret this finding as partially caused by the fact that many of the larger tumors, which would have had the highest risk of tumor progression if they had been treated with brachytherapy, were enucleated. However, it cannot be the full explanation as iodine-125 brachytherapy had been used for tumors with a larger mean thickness than the tumors that had been enucleated. We therefore hypothesized that a larger cause for the negative correlation is that the tumor regions closest to the optic nerve may have received too low radioactive doses when tumors were thin. As shown by Stöckel *et al.*, prescribing a minimum of 700 Gy to the tumor base regardless of its thickness may be a way to alleviate this (10). Our simulations indeed showed that tumor adjacent to the optic disc was likely underdosed when us-

ing the ruthenium-106 CCB or iodine-125 CCB plaque. The ruthenium-106 CCB plaque even delivers >400 Gy to larger areas of healthy tissue than to tumor tissue. The ruthenium-106 COB plaque irradiates much smaller areas of healthy tissue and covers the full circumference of the optic disc as well as the first 1.5 mm of the optic nerve sheath, at the cost of higher risk of radiation optic neuropathy.

This study has several limitations. First and foremost, our data was retrospective and treatments were not randomized. We cannot exclude that unknown factors influenced our results. The registry from which data was collected might not capture all tumor progressions, lack of regression, radiation side effects etc. accurately. We sought to limit the impact of missing data and misclassifications by careful examination of fundus photographs and clinical records. Further, ruthenium-106 was prescribed in higher doses to the tumor apex than iodine-125 (100 Gy vs. 80 Gy), due to concern for damage to surrounding tissues. If 100 Gy to the tumor apex had been prescribed with both radioisotopes, it is possible that the near-significant differences in risks for radiation side-effects and risk for treatment failure would have been significant. Last, it is possible that additional significant statistical differences would have appeared with a larger sample of patients.

In conclusion, ruthenium-106 brachytherapy with a notched COB plaque generates the highest radioactive doses to all areas of the tumor base and optic nerve sheath and the lowest doses to the anterior segment in the treatment of choroidal melanomas touching the optic disc. Regardless, brachytherapy of choroidal melanoma touching the optic disc entails a high risk for treatment failure with

more than 2 in 5 patients requiring secondary treatment. This risk is similar between iodine-125, ruthenium-106, plaque designs and if TTT has been used or not. The selection of treatment modality has however no influence on the risk for melanoma-related mortality, even if a tumor recurs after eye-preserving therapy.

### Disclosures

The authors declare that they have no competing interests.

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### Ethics approval and consent to participate

This study was approved by the regional ethical review board in Stockholm (reference number 2016/247-31/4; and amendment 2019-03485 from the Swedish Ethical Review Authority) and adhered to the tenets of the Declaration of Helsinki. Informed consent was waived as this is a retrospective chart review that did not affect the treatment or follow-up of patients and did not require new collection of sensitive data or access to individual patient medical records. Further, no new tissues were collected, sectioned, stained or otherwise processed.

### Consent for publication

Not applicable

### Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

### Authors' contributions

MF collected patient data. MA performed dose simulations. GS assessed fundus photographs and performed statistical analysis. All authors contributed to the writing of the manuscript, read and approved the final version.

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