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**BRACHYTHERAPY OF CHOROIDAL MELANOMAS LESS THAN 10 MM IN LARGEST
BASAL DIAMETER
Comparison of 10-mm and 15-mm Ruthenium Plaques**

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Running title: Brachytherapy of choroidal melanomas less than 10 mm in diameter

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29 **ABBREVIATIONS AND ACRONYMS**

- 30 BCVA Best corrected visual acuity
- 31 CI Cumulative incidence
- 32 COMS Collaborative Ocular Melanoma Study
- 33 DD Disk diameter
- 34 HR Hazard ratio
- 35 IOP Intraocular pressure
- 36 LBD Largest basal diameter
- 37 SE Standard error
- 38 TTT Transpupillary thermotherapy
- 39 WHO World Health Organization

40

ABSTRACT

Purpose: To compare tumor control, vision, and complications between patients with a choroidal melanoma <10 mm in largest basal diameter (LBD) irradiated with 10-mm or 15-mm ruthenium plaques.

Design: Retrospective comparative case series

Participants: One hundred sixty-four consecutive patients with a choroidal melanoma <10 mm in LBD, 76 and 88 treated with the 10-mm and 15-mm plaque, respectively, in 1998-2014 in a national ocular oncology service.

Methods: Diagnosis was based on growth or high-risk characteristics. The apical dose was 100-120 Gy aiming to deliver ≥ 250 Gy to the sclera. Plaque positioning was retrospectively modeled. An increase ≥ 0.3 mm in thickness and ≥ 0.5 mm in LBD indicated local recurrence. Outcomes were compared with cumulative incidence analysis and Cox regression. Median follow-up time for patients still alive was 8.4 years.

Main Outcome Measures: Recurrence rate, low vision, blindness, radiation maculopathy and optic neuropathy.

Results: Melanomas treated with the 10-mm plaque were smaller (median thickness, 1.9 vs 2.6 mm; LBD 7.1 vs 8.6 mm), and located closer to foveola (median, 2.0 vs 2.8 mm) than those treated with the 15-mm plaque ($P < 0.001$). The two plaques provided a safety margin in 43% vs 40% eyes, no safety margin, to guard foveola, in 17% vs 33%, and did not entirely cover tumor, mainly close to the disk, in 32% vs 18% of eyes, respectively ($P = 0.052$). The incidence of a local recurrence was comparable (13% vs 15% at 10 years; $P = 0.31$) and associated with plaque positioning (hazard ratio [HR] 2.81 for no safety margin, $P = 0.041$). At 5 years, the incidence of low vision was 14% vs 24%, and that of blindness 3% vs 6%. Distance to foveola was associated with loss of both levels of vision (HR, 0.65 vs 0.68 per mm, $P < 0.001$ vs $P = 0.004$). The incidence of radiation maculopathy was comparable (19% vs 18% at 5 years) whereas that of optic neuropathy tended to be higher with the 15-mm plaque (2% vs 9%; $P = 0.054$).

Conclusions: The 10-mm ruthenium plaque contributes to better visual preservation, particularly with tumors close to fovea, without increase in local recurrence rate and, therefore, may be

69 preferable to the 15-mm plaque.

70

Small choroidal melanomas are typically treated with eye-preserving treatments. Even small tumors are thought to be able to micrometastasize early, thus enucleation is no longer a generally accepted alternative.¹ According to a recent study by the European Ocular Oncology Group, a critical size may be as small as 3 mm in largest basal diameter (LBD), and melanomas that metastasize when still small are clinically indistinguishable by their high risk features from other melanomas of equal size.²⁻⁴ The primary aim when treating a small choroidal melanoma conservatively is to prevent local recurrences that are associated with a higher risk for metastases.⁵ An important secondary aim is to preserve as much useful vision as possible by minimizing side-effects, especially radiation maculopathy and optic neuropathy.

One way of reducing the risk of radiation-related side-effects is decreasing the size of the radioactive applicator. Compared with a 15-mm ruthenium plaque, which is widely used to irradiate small choroidal melanomas, the irradiated volume is smaller with a 10-mm plaque. Local tumor control rate of 91% at five years and cumulative incidence rate of avoiding low vision and blindness of 83% and 97%, respectively, in our previous non-comparative case series of 45 patients provided preliminary support for the use of the 10-mm ruthenium plaque in treating choroidal melanomas less than 10 mm in LBD.⁶ Our present comparative series explores whether or not the 10-mm plaque has an advantage over the 15-mm plaque in treating small choroidal melanomas of this size, adjusting for differences in baseline characteristics by multivariable regression analysis. We compare local tumor control, vision outcome, and side-effects between 76 and 88 consecutive patients who were managed with the 10-mm and 15-mm ruthenium plaques, respectively.

METHODS

Aims of the Study

The primary aim was to compare local tumor control, best corrected visual acuity (BCVA), and complications between eyes irradiated with the 10-mm and 15-mm ruthenium plaque, in a population-based consecutive series of patients with a choroidal melanoma less than 10 mm by

LBD. The secondary aim was to compare mortality between the two groups.

Inclusion Criteria

Eligible to our study were patients diagnosed with a choroidal melanoma less than 10 mm in LBD between October 1998 and December 2014 who were scheduled to receive a 10-mm (CCX) or 15-mm (CCA) ruthenium plaque (Eckert & Ziegler BEBIG GmbH, Berlin, Germany). The LBD was based on indirect ophthalmoscopy and B-scan echography (I3 System-ABD; Innovative Imaging, Sacramento, CA). The 10-mm ruthenium plaque came into use in 1998 in the Ocular Oncology Service, Department of Ophthalmology, Helsinki University Hospital, Finland, a national referral center for uveal melanomas, and gradually became the plaque of choice for tumors of this size, especially those close to the foveola. In the early years, we more often chose the 15-mm plaque for tumors close to 10 mm in LBD, and the 15-mm plaque additionally was used for 13 patients to expedite treatment when the 10-mm plaque was in use for another patient. The study followed the tenets of the Declaration of Helsinki, and was approved by the institutional review board.

We reviewed the database and identified 234 patients with a choroidal melanoma less than 10 mm in LBD of whom 76 had been scheduled for the 10-mm and 88 for the 15-mm plaque ruthenium radiotherapy. One patient received the 10-mm plaque as secondary treatment after regrowth of a tumor treated 20 years earlier with three sessions of argon laser photocoagulation, and one patient received the 15-mm plaque 7 months after photodynamic therapy. All tumors irradiated with the 10-mm plaque and 16 of the 88 treated with the 15-mm plaque were T1aN0M0, stage I, and the remaining ones T2aN0M0, stage IIA, by the American Joint Committee on Cancer (AJCC) Tumor, Node, Metastasis (TNM) System, 8th edition.⁷ By Collaborative Ocular Melanoma Study criteria, 65 (86%) and 60 (68%) tumors, respectively, would have been classified as small.⁸

An additional 70 tumors of the same size were scheduled for other treatments (Fig.1 and Table 1, available at <http://www.aaojournal.org>, which show types of various plaques used and tumor dimensions by plaque type).

Clinical Evaluation

We measured the BCVA using a test-type projector (Rodavist 2 and 524; Rodenstock GmbH, Ottobrunn, Germany) in even decimals from 1.0 (20/20) to 0.1 (20/200) plus 0.05 (20/400). BCVA worse than 20/400 was recorded as counting fingers at 2, 1, and 0.5 m, hand movement, light perception, and no light perception. We used biomicroscopy, indirect ophthalmoscopy and fundus photographs to localize the tumor margins, to estimate the distance from the posterior tumor margin to the optic disk and foveola, and to evaluate the growth pattern, presence of subretinal fluid, and presence of orange pigment.

We treated the patients if they had a presumed small choroidal melanoma because it had been observed to grow (37%) or had high-risk characteristics predictive of growth (Table 2): thickness over 2 mm in 93 (57%) eyes, subretinal fluid in 103 (63%), symptoms in 79 (48%), orange pigment in 92 (56%), and tumor margin within 2 disk diameters (DD) of the optic disk in 81 (49%) of which 4 (2%) touched the disk margin (Table 2). Symptoms included decreased vision, a visual field defect, flashes, floaters, and metamorphopsia. Other risk characteristics were ultrasound hollowness in 113 (69%), absence of a surrounding halo in 161 (98%), and absence of drusen in 113 (69%). The range of observed growth was 0.1-2.3 mm (median, 0.5 mm) in thickness and 0.1-6.0 (median, 1.0 mm) in LBD. Twelve (7%) tumors were treated without any risk characteristics because of growth. Two (2%) patients were treated without risk factors or growth. The first one had a tumor that had not been seen during regular visits for glaucoma and was hollow by ultrasound. The second one had ruptured Bruch's membrane.

Brachytherapy

The 10-mm and 15-mm plaques have a physical diameter of 11.6 and 15.3 mm, respectively, and a radius of curvature of 12 mm. The corresponding diameters of the irradiation windows are 10.0 and 13.8 mm before reshaping the applicator to spherical contour. The window is surrounded by a 0.75-mm-wide inactive border. In the spherical form, the cord diameter of the radiation window is 9.4 and 12.9 mm, respectively, surrounded by a penumbra of scatter radiation,

which facilitates eccentric placement to limit irradiating adjacent tissues.^{9,10} The prescription point was thickness plus 1 mm for the sclera. The apical dose was 100 to 120 Gy to tumor apex aiming to deliver a minimum scleral dose of 250 Gy. Treatment times and doses were calculated from the central axis depth dose curve (Table 3) and calculations were based on the Bebig Plaque Simulator data (version 5.3.7.). The inferior oblique muscle was detached in 26 (34%) eyes with the 10-mm and 39 (44%) eyes with the 15-mm plaque when the tumor was located in the macular area. Three experienced ocular oncologists performed the treatments. The surgical technique has been described previously.⁶

Assessment of Local Tumor Control, Metastasis, Vision, and Side-effects

We followed patients prospectively at 3, 6, and 12 months and every 6 months until 3 to 4 years. Thereafter, 8 patients were seen annually in a central hospital, 19 in other universities, and the remaining ones in our service. We used biomicroscopy, indirect ophthalmoscopy, fundus photography, and B-scan echography to assess tumor control. We coded recurrences as marginal, vertical, diffuse (marginal+vertical), or extrascleral.¹¹ An unequivocal change of at least 0.3 and 0.5 mm in thickness and LBD indicated a vertical and marginal recurrence, respectively.

We retrospectively modeled the location of the plaque to facilitate determining the reasons for local recurrence. We used the radiation and diathermy scars, if visible, on post-treatment fundus photographs together with the surgical notes to digitally draw on a color fundus photograph a circle corresponding to the radiation window, presuming the average diameter of the optic disk to be 1.5 mm. We coded the location of the radiation window relative to tumor margins as covering the entire tumor with a safety margin, being parallel, or not covering the entire tumor.⁶

We performed liver function tests and upper abdominal ultrasonography at the time of diagnosis and annually thereafter, and a chest radiogram at diagnosis. Suspicious lesions were verified and staged with computed tomography, magnetic resonance imaging, or both. Histopathological confirmation was taken with a fine or core needle biopsy. Causes of deaths were verified from death certificates and patient charts.

We assessed the visual outcome following the conventions of the Collaborative Ocular Melanoma Study (COMS).¹² Measurements below 20/1,600, such as counting fingers or hand movement, were set to 20/1,600. Enucleated eyes and eyes with no light perception were counted as having 20/2,500 vision. We analyzed low vision (BCVA <20/65) and blindness (BCVA <20/400) according to the World Health Organization (WHO)¹³ standard definitions. Loss of BCVA was recorded when confirmed at the next review. If a measurement had not been made at every review, we considered the BCVA to be the mean of the previous and the next visit. Otherwise, we coded the data as missing. We assessed side-effects as outlined in a previous study from our service.¹⁴ Maculopathy was categorized as radiation maculopathy or other maculopathy (recurrent tumor, radiation scar, epiretinal membrane, tumor-related lipid exudation, and exudative retinal detachment).

Statistical Methods

We collected follow-up data prospectively up to the date of analysis on December 31, 2017 and analyzed them with Stata (Release 15; Stata Corp, College Station, TX). We analyzed regression in tumor thickness at 6-month intervals. We used cumulative incidence analysis that takes competing risks into account to provide estimates that would be most useful in clinical counseling in comparing outcomes, and compared groups with Gray's k-sample test. We used Fisher's exact test in comparing dichotomous variables, non-parametric test for trend in exploring differences between two independent groups for ordinal variables, and Kruskal-Wallis between two or more independent groups for continuous variables. All tests were 2-tailed and $P < 0.05$ was statistically significant.

We calculated mean BCVA after transformation to logarithmic scale, stratified by factors associated with vision outcomes at 6-month intervals.

We used multivariable Cox regression analysis to estimate the hazard ratio (HR), adjusting the effect of plaque type for previously identified explanatory and confounding variables for local recurrence and losing BCVA of 20/65 and 20/400. Variables significant at the univariable level

were entered into bi- and trivariable models. The assumption of proportional hazards was tested by the method of Therneau and Grambsch¹⁵ both globally and for individual covariables in the model. Independent variables were allowed in the model if $P < 0.10$. Models were compared using the likelihood ratio test¹⁶. The best fitting models are reported as final ones. We performed sensitivity analyses of the final Cox regression models for the three main outcomes – local tumor recurrence and development of low vision and blindness – by restricting LBD to less than 9 mm to balance the distribution of tumor diameter between the two study groups to further guard against the possibility that more frequent irradiation of tumors with LBD between 9.0 and 9.9 mm with the 15-mm plaque might have biased our estimates.

To guide the reader, we provide *post hoc* estimates of HR likely to be detected with 0.80 power for our three main outcomes, calculated for log-rank test using the Schoenfeld method. We set the significance level at 0.05, and the sample sizes and 10-year survival proportions to match those observed in each analysis.

RESULTS

The median age at diagnosis (65 vs. 63 years; $P = 0.59$, Kruskal-Wallis test) and the BCVA ($P = 0.55$, nonparametric test for trend) were comparable between the two groups (Table 4, available at <http://www.aaojournal.org>, which shows characteristics of patients and tumors). At the time of diagnosis, 6 (8%) and 6 (7%) eyes had low vision, and 1 (1%) and 3 (3%) were blind by WHO criteria,¹³ in patients treated with the 10-mm and 15-mm plaque, respectively.

The melanomas treated with the 10-mm plaque were thinner (median, 1.9 vs 2.6 mm, $P < 0.001$, Kruskal-Wallis test) and had a smaller LBD (median, 7.1 vs 8.6 mm, $P < 0.001$) than those treated with the 15-mm plaque (Fig. 2A-B). Distance from the posterior tumor margin to the foveola was shorter in eyes treated with the 10-mm plaque (median, 2.0 vs 2.8 mm, $P < 0.001$, Fig. 2C) so that the posterior tumor margin involved the foveola in 20 (26%) eyes treated with the 10-mm plaque and 17 (19%) treated with the 15-mm plaque and extended to within 2 DD of it in 50

(66%) eyes treated with 10-mm plaque and 50 (57%) treated with 15-mm plaque. The distance from the tumor margin to the optic disk was comparable (median for both 3.0 mm, Fig.2D) as was extent of subretinal fluid ($P=0.59$, nonparametric test for trend).

Plaque Positioning

According to the surgical charts, the physical 10-mm and 15-mm plaque covered the tumor with a safety margin in 25 (33%) and 50 (57%) eyes, was eccentric in 28 (37%) and 28 (32%) eyes, and did not entirely cover the tumor in 22 (29%) and 10 (11%) eyes, respectively ($P=0.002$, nonparametric for trend). By retrospective modeling of coverage by the radiation window differed to a lesser extent ($P=0.052$). The corresponding numbers were 33 (43%) and 35 (40%), 13 (17%) and 29 (33%), and 24 (32%) and 16 (18%). Modeling of plaque location was unsuccessful in 6 (8%) and 7 (8%) eyes treated with the 10-mm and 15-mm plaque, respectively. No adverse events occurred during the surgical procedure.

Tumor Regression and Local Recurrence

The follow-up time for patients who were still alive was comparable (median, 8.1 years, range 3.0–18.8; and 8.9 years, range 1.1–17.9; $P=0.45$, Kruskal-Wallis test). By 3 years, tumor thickness had reduced equally in the two groups (median, 42% and 35%; Fig.3A). A local recurrence was detected in 9 and 16 patients after a median follow-up of 1.5 (range, 0.5-6.5) and 3.0 (range, 0.3-14.0) years, respectively (Table 5, available at <http://www.aaojournal.org>, which shows details of all recurrences). The cumulative incidence of developing a local recurrence (Fig.3B) was comparable, 9% (95% CI, 4-17) and 13% (95% CI, 7-20) at 5 years and 13% (95% CI, 6-21) and 15% (95% CI, 8-23) at 10 years, respectively ($P=0.31$, Gray's k-sample test). With 164 patients, we had 0.80 power, *post hoc*, to detect a HR of 2.4 as statistically significant.

By univariable Cox regression, a local recurrence was associated with plaque positioning (HR 2.81 for plaque not covering the tumor with a safety margin, $P=0.041$; Table 6). In bivariable models positioning the plaque predicted a local tumor recurrence (HR 2.72, $P=0.048$). In univariable models stratified by plaque size the hazards ratios (HR=2.31 for the 10-mm plaque and

HR=2.99 for the 15-mm plaque) remained comparable (Table 6, and 7 available at <http://www.aaojournal.org>, which shows alternative models). The models suggest that the combined effect derived predominantly from treatment with the 15-mm plaque. Sensitivity analysis, restricting LBD to less than 9 mm, showed that the HR for plaque size remained consistent with that in the full sample (HR, 1.91 vs 2.03, respectively) whereas that for positioning the plaque became less influential (HR, 1.98 vs 2.72; Fig. 4 and Table 8, available at <http://www.aaojournal.org>, which shows the size distribution between two groups and comparison of HR in final models, respectively).

The recurrences were treated with a secondary iodine plaque, except one that was retreated with a ruthenium plaque and two that received transpupillary thermotherapy (TTT; Table 5, available at <http://www.aaojournal.org>, which shows details of all recurrences). One of 9 patients treated with the 10-mm plaque and 4 of the 16 (25%) patients treated with the 15-mm plaque developed additional recurrences mostly managed with TTT (Table 5).

Metastasis and Survival

Of patients treated with the 10-mm and 15-mm plaque, 16 and 28 died during follow-up, 3 and 7 of them of metastatic choroidal melanoma, respectively. One patient was alive with metastases after a local recurrence (Table 5, case 4, available, <http://www.aaojournal.org>). Nine of the 11 metastases were histologically verified and 2 were diagnosed with imaging (a solitary brain tumor classified as a possible metastasis, and multiple hepatic lesions, a fine needle aspiration biopsy of which failed). All four patients who developed metastases after the 10-mm plaque, and 4 of the 7 patients treated with the 15-mm plaque had experienced a local recurrence a median of 1.8 years (range, 0-5.7) and 1.5 years (range, 0-3.5) before metastases, respectively. Conversely, 4 of 9 (44%) and 4 of 16 (25%) patients with a local recurrence later developed metastases, respectively.

The cumulative incidence of developing metastases was 4% (95% CI, 1-10) at 5 and 10 years after treatment with the 10-mm plaque, and 6% (95% CI, 2-13) at 5 years and 10% (95% CI, 4-19) at 10 years after treatment with the 15-mm plaque ($P=0.50$, Gray's k-sample test). The

cumulative incidence estimate of all-cause mortality was 10% (95% CI, 4-18) and 9% (95% CI, 4-17) at 5 years, and 24% (95% CI, 13-37) and 29% (95% CI, 19-40) at 10 years, respectively (Fig.3C; $P=0.24$), and of melanoma-related mortality 3% (95% CI, 1-8) at 5 and 10 years and 2% (95% CI, 0.5-7) at 5 years and 8% (95% CI, 3-15) at 10 years, respectively (Fig.3D), percentages that were comparable and far exceeded by deaths from other causes. The time from treatment of the primary tumor to metastases (median, 4.6 vs 4.5 years; $P=0.85$, Kruskal-Wallis test) and survival after metastases (median, 3.6 vs 6.1 years; $P=0.73$) were also comparable between the two groups.

Preservation of Vision

The median BCVA at 5 years was 20/32 and 20/30, and at 10 years 20/40 and 20/40 in eyes treated with the 10-mm and 15-mm plaque, respectively. Five years after diagnosis, the BCVA was at least 2 lines better in 5 (8%; 95% CI, 4-7) and 11 (16%; 95% CI, 8-16) eyes, within 1 line of pretreatment BCVA in 22 (37%; 95% CI, 16-33) and 18 (26%; 95% CI, 13-26) eyes, and at least 2 lines worse in 33 (55%; 95% CI, 24-50) and 39 (57%; 95% CI, 28-56) eyes ($P=0.88$, non-parametric test for trend), respectively.

Tumor thickness over 3.0 mm was associated with loss of BCVA, more notably after the 10-mm plaque (Fig.5A, B), whereas increasing LBD did not predict loss of vision (Fig.5C, D). Location of the tumor margin less than 1.5 mm from foveola (Fig.5E, F) was associated with mild loss of BCVA, especially after treatment with the 15-mm plaque, as was a distance of less than 4.5 mm from the optic disk with the 15-mm plaque (Fig.5G, H).

The cumulative incidence of losing 20/65 vision in 70 and 82 eyes that had at least this BCVA at diagnosis was 14% (95% CI, 7-24) and 24% (95% CI, 15-34; Fig.3E), and that of losing 20/400 vision in 75 and 85 eyes was 3% (95% CI, 0.6-10) and 6% (95% CI, 2-13; Fig.3F) at 5 years with the 10-mm and 15-mm plaque, respectively. The corresponding incidences at 10 years after diagnosis were 21% (95% CI, 11-33) and 30% (95% CI, 20-41) for low vision, and 14% (95% CI, 6-25) and 13% (95% CI, 6-23) for blindness, respectively. With 152 and 160 patients, we had 0.80 power, *post hoc*, to detect a HR of 2.0 and 2.3 as significant regarding developing low vision and

blindness, respectively.

By univariable Cox regression, low vision and blindness were associated with distance to foveola (HR, 0.65 and 0.68 for each 1 mm increase for the 10-mm and 15-mm plaque, $P<0.001$ and $P=0.004$, respectively; Table 9), baseline BCVA (HR, 0.16 and 0.3 for each 0.1 logMAR decrease, $P<0.001$ and $P=0.043$, respectively), and with tumor thickness (HR, 1.31 and 1.53 for each 1 mm increase, $P=0.077$ and $P=0.025$, respectively). Of bivariable models that included plaque size, the one with distance to the foveola best predicted low vision (HR, 0.64 for each 1 mm increase in distance, $P<0.001$; Table 9). A trivariable model that additionally included BCVA at baseline or tumor thickness did not provide a significantly better fit ($P=0.23$ and $P=0.094$, respectively, likelihood-ratio test). Distance to the foveola also was independently associated with developing blindness in a bivariable model (HR, 0.68 for each 1 mm decrease in distance, $P=0.004$), and a trivariable model that additionally included tumor thickness fitted best with the data ($P=0.010$, likelihood-ratio test).

Sensitivity analysis, restricting LBD to less than 9 mm, showed that the HR for plaque size remained close to that in the full sample (HR, 1.56 vs 1.79, respectively) as did that for tumor distance to the foveola (HR, 0.60 vs 0.64 for a 1-mm change) for developing low vision (Fig. 4 and Table 8, available at <http://www.aaojournal.org>, which shows the size distribution between two groups and comparison of HR in final models, respectively). Because plaque size was not nearly a significant predictor of developing blindness ($P=0.69$), its HR estimate is unstable in the sensitivity analysis and the full sample. The effect of tumor distance to the foveola is estimated to be slightly stronger and the effect of tumor thickness slightly less (Table 8).

Enucleation and Cosmetic Outcome

No secondary enucleation was performed after primary treatment. One patient developed extraocular extension after treatment for multiple local recurrences (Table 5, case 4, available at <http://www.aaojournal.org>) and one eye was blind and painful eye from secondary glaucoma after vitrectomy for vitreous hemorrhage following secondary brachytherapy for two local recurrences

(Table 5, case 10), leading to enucleation. All other eyes had normal cosmesis at last follow-up.

Treatment-Related Side-effects

Cataract. The cumulative incidence of cataract developing or progressing, never considered to be radiation-related, was comparable (50% vs. 58% at 10 years after treatment with the 10-mm and 15-mm plaque, respectively).

Iris neovascularization. Two patients developed iris neovascularization after secondary irradiation for a local recurrence (Table 5, available at <http://www.aaojournal.org>; case 1 and 16).

Glaucoma. Two patients developed glaucoma after treatment with the 10-mm plaque. The first one had had radiation maculopathy and tumor-related lipid exudation, and intraocular pressure remained elevated after vitrectomy for a rhegmatogenic retinal detachment. The second one developed open angle glaucoma. The cumulative incidence of glaucoma developing was 1% (95% CI, 0.1-6) at 5 and 10 years after treatment.

Vitreous hemorrhage. Vitreous hemorrhage developed in 4 eyes a median of 1.9 (range, 0.1–12) years after treatment with the 10-mm plaque, and in 9 eyes a median of 2.1 (range, 0.1–13) years after the 15-mm plaque. The cumulative incidence rates of 4% (95% CI, 1-10) at 5 and 10 years, and 6% (95% CI, 2-12) at 5 years and 12% (95% CI, 5-21) at 10 years, respectively, were comparable ($P=0.25$).

Maculopathy. After the 10-mm and 15-mm plaque, 17 and 20 eyes developed non-proliferative radiation maculopathy, and 14 and 13 eyes developed other types of maculopathy, respectively (Table 10). The cumulative incidence of developing both radiation maculopathy, 19% (95% CI, 11-28) and 18% (95% CI, 11-27) at 5 years and 24% (95% CI, 15-35) and 22% (95% CI, 14-32) at 10 years, respectively, and other maculopathy, 4% (95% CI, 1-11) and 1% (95% CI, 0.1-6) at 5 years and 10% (95% CI, 4-21) and 10% (95% CI, 4-19) at 10 years, were comparable (Fig. 3G).

Optic neuropathy. One eye treated with the 10-mm plaque for a tumor located 4 mm from the optic disk developed radiation optic neuropathy 3 years and 8 months after irradiation, whereas

7 eyes treated with the 15-mm plaque developed this side-effect a median of 3.1 years (range, 2.0-5.3) after irradiation of a tumor when its margin was a median of 2 mm (range, 0.3-2.5) from the disk. The cumulative incidence of developing optic neuropathy was 1% (95% CI, 0.1-7) and 8% (95% CI, 3-15) at 5 and 10 years, respectively (Fig. 3H).

DISCUSSION

The more fundamental of the two questions that our study set to answer was whether or not treating a choroidal melanoma 10 mm or less in LBD with the 10-mm rather than with the more commonly used 15-mm ruthenium plaque is safe, using local tumor recurrence rate as the primary endpoint. The unadjusted rate by 5 and 10 years was 4 and 2 percentage points higher, respectively, with the 15-mm plaque, a non-significant difference by cumulative incidence analysis. After 10 years, three diffuse recurrences occurred in eyes treated with the 15-mm plaque, whereas none of the 29 melanomas treated with the 10-mm plaque still under follow-up at 10 years recurred later. This might have reflected either the larger median thickness and LBD of the tumors treated with the 15-mm plaque or the higher median dose to tumor apex with the 10-mm plaque, resulting from our rule to deliver a minimum scleral dose of 250 Gy,⁶ more often realized with the comparatively thinner tumors irradiated with the 10-mm plaque. However, neither tumor size nor dose to apex was associated with local recurrence in multivariable modeling. Moreover, a sensitivity analysis that restricted tumor size to less than 9 mm to equalize size distribution returned a similar HR for plaque size than the main analysis.

The variable that expectedly predicted more frequent recurrence, adjusted to plaque size, was plaque positioning both in the main and in the sensitivity analysis. Both plaques were planned in about 40% of eyes to be parallel with the posterior tumor margin to reduce dose to the foveola. Moreover, more than 30% of the tumors were located within 2.25 mm of the margin of the optic disk and, because of the 1.5 mm thick optic nerve sheath and the non-irradiating 0.75 mm rim of the plaque, the plaque could not physically cover the entire tumor. In the latter eyes, the round plaques

were chosen to limit radiation to the optic disk as compared to notched ones. These approaches,⁶ which naturally necessitate close follow-up and immediate retreatment should evidence of a local recurrence emerge, also explains the 15% overall 10-year recurrence rate as compared to our usual rate of 10% or smaller. The 15-mm plaque covered the tumor as often as the 10-mm plaque, and multivariable analysis also showed that plaque positioning did not completely explain why the 15-mm plaque was associated with more recurrences than the 10-mm plaque. In summary, we can confidently conclude that use of the 10-mm plaque, which was preferential in our practice, most likely did not increase the rate of local recurrences.

Only a few previous studies have specifically addressed brachytherapy of choroidal melanomas in this size range. After brachytherapy with palladium, a gamma ray emitter, complete local tumor control was reported for tumors less than 10-mm in LBD mainly with round COMS-type plaques of unspecified size.¹⁷ In contrast to our series, all tumors were 1.5-2.4 mm in thickness. We treated 37 and 23 tumors of this size with the 10-mm and 15-mm plaque, and 1 and 3 of them developed a local recurrence, respectively. A further difference was that 39 (54%) of the 72 tumors treated with palladium were located within 6.0 mm of the optic disk and foveola, as compared to 34 (92%) of the 37 and 22 (96%) of the 23 tumors treated with the 10-mm and 15-mm ruthenium plaque, respectively.

Rates of metastasis were, as expected, comparable with both plaques and with 31 patients more and a longer follow-up time as compared with our previous report of 45 patients⁶ treated with the 10-mm plaque, the 10-year rate is still 4%. The melanoma-related mortality was about 8% and not higher than the 6-10% estimate for small (T1a, stage I) choroidal melanomas in general^{18,19} even with the 15-mm plaque, despite the fact that most tumors irradiated with it were T2a, stage IIA.

The second question that we set to answer was whether or not treating a choroidal melanoma 10 mm or less in LBD with the 10-mm rather than with the 15-mm ruthenium plaque will conserve more vision, using as primary endpoints loss of 20/65 and 20/400 BCVA that correspond to development of low vision and blindness by WHO criteria, respectively. Unadjusted rates of

losing 20/400 vision as evaluated by cumulative incidence analysis appeared to be equal for both plaques, whereas 20/65 vision seemed to be more frequently conserved with the 10-mm plaque for the first 10 years, after which this difference vanished. Multivariable analysis confirmed that plaque size was not significant when predicting blindness, which was determined by distance of the tumor margin to the foveola and tumor thickness, controlling for plaque size.

As regards low vision, the initial difference could have reflected the larger thickness and LBD of the melanomas treated with the 15-mm plaque. Multivariable modeling showed, however, that instead of tumor size, distance of its margin from the foveola in addition to plaque size was the strongest independent bivariable indicator of development of low vision, and more so than the BCVA of the treated eye at baseline. The risk of losing 20/65 vision was 1.79 times higher with the 15-mm plaque, controlling for distance to the foveola. Adding tumor thickness did not significantly improve model fit but suggested that the effect of plaque size was partially mediated by different tumor thicknesses between the two plaques. Again, a sensitivity analysis that restricted tumor size to less than 9 mm returned a similar HR for plaque size than the main analysis. Even if the difference in vision would be marginal, the radiation scar will be smaller in area with the 10-mm plaque. Our conclusion is that use of the 10-mm plaque contributed to retaining reading vision in the treated eye, but could not prevent blindness in an eye with a relatively higher tumor located close to the foveola, at least during the first 10 years after treatment.

Considering the mean BCVA over the first three years according to COMS conventions,¹² loss of vision from the baseline was notable when tumor thickness exceeded 3.0 mm, whereas increasing LBD did not lead to vision loss. Vision remained relatively stable when treating posterior tumors located more than 1.5 mm away from foveola and the optic disk with either plaque.

The unadjusted rate of developing radiation maculopathy was equal with both plaques (19% and 18% at 5 years) as estimated by cumulative incidence analysis, and thus lower than in our earlier smaller series (28%).⁶ The unadjusted rate of developing radiation optic neuropathy was higher with the 15-mm than the 10-mm plaque, but still only 9%. We confirm that radiation optic

neuropathy is a rare side-effect after ruthenium brachytherapy of choroidal melanomas 10 mm of less in diameter with the 10-mm plaque, even when managing posterior tumors. The complete local tumor control with palladium plaques appears to have been offset by a higher rate of radiation maculopathy (43%) and optic neuropathy (21%),¹⁷ as compared with our results.

A limitation of our retrospective study is that a few patients had partially missing data at individual visits to referring hospitals during their later follow-up. Our study was not randomized, and the two groups were not entirely matched, and our series was not powered to detect increases in HR smaller than 2.0-2.4. Plaques were not chosen systematically to patients according to tumor characteristics. Multivariable analysis was used to adjust for these differences, which reduced but does not eliminate bias entirely, and sensitivity analysis that restricted LBD to obtain a more similar distribution supported the observed effect sizes. These limitations taken into account, the outcomes were similar to our earlier pilot report of treatment with the 10-mm plaque.⁶ The results taken together favor continued use of the 10-mm plaque for small choroidal melanomas less than 10 mm in LBD. The local tumor recurrence rate was not worse than after the 15-mm plaque with suggestion of a higher chance of retaining 20/65 vision when a small choroidal melanomas less than 10 mm in LBD is located close to the macula and optic disk.

REFERENCES

1. Eskelin S, Pyrhönen S, Hahka-Kemppinen M, Tuomaala S, Kivelä T. A prognostic model and staging for metastatic uveal melanoma. *Cancer*. 2003;97:465-475.
2. Shields CL, Shields JA, Kiratli H, De Potter P, Cater JR. Risk factors for growth and metastasis of small choroidal melanocytic lesions. *Ophthalmology*. 1995;102:1351-1361.
3. Shields CL, Shields JA. Clinical features of small choroidal melanoma. *Curr Opin Ophthalmol*. 2002;13:135-141.
4. Jouhi S, Jager MJ, de Geus SJR, et al. The Small Fatal Choroidal Melanoma Study. A Survey by the European Ophthalmic Oncology Group. *Am J Ophthalmol*. 2019;202:100-108.
5. Jampol LM, Moy CS, Murray TG, et al. The COMS randomized trial of iodine 125 brachytherapy for choroidal melanoma: IV. Local treatment failure and enucleation in the first 5 years after brachytherapy. COMS report no. 19. *Ophthalmology*. 2002;109:2197-2206.
6. Salkola S, Heikkonen J, Eskelin S, Kivelä T. Management of choroidal melanomas less than 10 mm in largest basal diameter with a 10-mm ruthenium plaque. *Retina*. 2014;34:2110-2120.
7. Kivelä T, Simpson R, Grossniklaus HE, et al. Uveal Melanoma. In: Mahul BA, ed. *AJCC Cancer Staging Manual*. 8 ed. Chicago: Springer; 2017:805-817.
8. The Collaborative Ocular Melanoma Study Group. Factors predictive of growth and treatment of small choroidal melanoma: COMS Report No. 5. *Arch Ophthalmol*. 1997;115:1537-1544.
9. Russo A, Laguardia M, Damato B. Eccentric ruthenium plaque radiotherapy of posterior choroidal melanoma. *Graefes Arch Clin Exp Ophthalmol*. 2012;250:1533-1540.
10. Pe'er J. Ruthenium-106 brachytherapy. *Dev Ophthalmol*. 2012;49:27-40.

- 477 11. Harbour JW, Char DH, Kroll S, Quivey JM, Castro J. Metastatic risk for distinct patterns of
478 postirradiation local recurrence of posterior uveal melanoma. *Ophthalmology*.
479 1997;104:1785-1792; discussion 1792-1783.
- 480 12. The Collaborative Ocular Melanoma Study Group. The Collaborative Ocular Melanoma
481 Study (COMS) randomized trial of pre-enucleation radiation of large choroidal melanoma
482 I: characteristics of patients enrolled and not enrolled. COMS report no. 9. *Am J*
483 *Ophthalmol*. 1998;125:767-778.
- 484 13. Best A, Corn A. The management of low vision in children: Report of the 1992 World
485 Health Organization consultation. *J Vis Impair*. 1992;87:307-309.
- 486 14. Puusaari I, Heikkonen J, Kivelä T. Ocular complications after iodine brachytherapy for
487 large uveal melanomas. *Ophthalmology*. 2004;111:1768-1777.
- 488 15. Therneau TM, Grambsch PM. *Modeling Survival Data: Extending the Cox Model*. New
489 York: Springer; 2000; 127-152
- 490 16. Hosmer D, Jr, Lemeshow S. *Applied Survival Analysis. Regression Modeling of Time to*
491 *Event Data*. New York: Wiley; 1999; 132-168
- 492 17. Semenova E, Finger PT. Palladium-103 radiation therapy for small choroidal melanoma.
493 *Ophthalmology*. 2013;120:2353-2357.
- 494 18. Kujala E, Damato B, Coupland SE, et al. Staging of ciliary body and choroidal melanomas
495 based on anatomic extent. *J Clin Oncol*. 2013;31:2825-2831.
- 496 19. AJCC Ocular Oncology Task Force. International Validation of the American Joint
497 Committee on Cancer's 7th Edition Classification of Uveal Melanoma. *JAMA*
498 *ophthalmology*. 2015;133:376-383.

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Figure 2. Frequency distribution of tumor thickness (**A**), largest basal diameter (**B**), distance to foveola (**C**), and distance to optic disk margin (**D**) of choroidal melanomas less than 10 mm in largest basal diameter of which 76 were irradiated with the 10-mm (*black*) and 88 with the 15-mm (*red*) ruthenium plaque.

Figure 3. Percentage reduction in thickness for 76 and 88 choroidal melanomas less than 10 mm in largest basal diameter irradiated with the 10-mm (*black*) and 15-mm (*red*) ruthenium plaque, respectively (**A**). Cumulative incidence of local recurrence (**B**), death (**C**), melanoma-related death (**D**), low vision (**E**) and blindness (**F**) by World Health Organization definitions, maculopathy (**G**), and optic neuropathy (**H**). The main competing risks are also plotted: death of any cause (**C,B,F-H**), death of causes other than melanoma (**D**), and other maculopathy (**G**). Crossbars show 95% confidence interval, and ticks censored observations. Numbers are patients at risk. BCVA, best corrected visual acuity.

Figure 5. Mean visual acuity for 76 and 88 patients with a choroidal melanoma less than 10 mm in largest basal diameter irradiated with the 10-mm (*black*) and 15-mm (*red*) ruthenium plaque, respectively, stratified by tumor thickness (**A,B**), largest basal tumor diameter (**C,D**), distance of tumor margin to foveola (**E,F**), and optic disk (**G,H**). Crossbars show 95% confidence interval, omitted for groups with less than 7 patients.

Table 10. Type of Maculopathy for 164 eyes with Small Choroidal Melanomas Less than 10 mm in Largest Basal Diameter Irradiated with the 10-mm and 15-mm Ruthenium Plaque

Plaque	Recurrent tumor	Radiation maculopathy	Radiation scar	Epiretinal membrane	Tumor-related lipid exudation	Exudative retinal detachment
10-mm (n=76)	4*	17	3	6	1	0
15-mm (n=88)	5 [†]	20	3	3	1	1

P = 0.87, Fisher's exact test

* Two primary tumors were sub-foveal at presentation

[†] One primary tumor was sub-foveal at presentation

Table 2. Risk Characteristics for Growth in 164 the Small Choroidal Melanomas Less than 10 mm in Largest Basal Diameter Managed with 10-mm and 15-mm Ruthenium Plaque

Risk Characteristics	10-mm n=76	15-mm n=88	P	Observed Growth		
				10-mm n=29	15-mm n=32	P
Thickness over 2 mm	30 (39)	63 (72)	<0.001*	6 (21)	19 (59)	0.004*
Subretinal fluid	48 (63)	55 (63)	0.99*	8 (28)	11 (34)	0.81*
Symptoms	40 (53)	39 (44)	0.35*	8 (28)	5 (16)	0.35*
Orange pigment	47 (62)	45 (51)	0.21*	13 (45)	11 (34)	0.44*
Margin						
touching disk	3 (4)	1 (1)	0.34*	1 (1)	0 (0)	0.48*
within 2 DD from disk	40 (53)	41 (47)	0.53*	8 (28)	14 (44)	0.19*
Number of characteristics						
0	9 (12)	5 (6)	0.87†	8 (28)	4 (13)	0.12†
1	9 (12)	10 (11)		7 (24)	7 (22)	
2	16 (21)	17 (19)		8 (28)	11 (34)	
3	14 (18)	30 (34)		4 (14)	9 (28)	
4	19 (25)	21 (24)		2 (7)	1 (1)	
5	9 (12)	5 (6)		0 (0)	0 (0)	

DD = disk diameters; *Fisher's exact test; †non-parametric test for trend

Table 3. Delivered Dose, Dose Rate and Treatment Time for 164 Small Choroidal Melanomas Less than 10 mm in Largest Basal Diameter Irradiated with the 10-mm and 15-mm Ruthenium Plaque*

Plaque	Apex, median (range)		Sclera, median (range)		Treatment time, (h)
	Dose, (Gy)	Dose rate, (cGy/h)	Dose, (Gy)	Dose rate, (cGy/h)	
10-mm	117 (80-197)	11.5 (3.1-42.4)	346 (201-824)	36.0 (8.9-94.4)	98 (28-334)
15-mm	105 (79-183)	10.6 (3.4-40.0)	340 (169-1015)	38.0 (12.6-92.1)	102 (31-269)
P [†]	0.060	0.66	0.65	0.89	0.89

*The standard prescription dose was either 100 or 120 Gy to tumor apex depending on the thickness of the tumor, aiming to deliver a minimum dose of 250 Gy to the sclera

[†]Kruskal-Wallis test

Table 6. Cox Proportional Hazards Regression of Time to Local Recurrence of 164 Patients with a Small Choroidal Melanoma Irradiated with the 10-mm and 15-mm Ruthenium Plaque

Variable	Coefficient (SE)	Wald χ^2	P	Hazard Ratio (95% CI)
<i>Univariable analysis</i>				
Plaque [*]	0.435 (0.417)	1.09	0.30	1.55 (0.68-3.50)
Thickness [†]	0.255 (0.191)	1.78	0.18	1.29 (0.89-1.88)
LBD [‡]	0.128 (0.153)	0.70	0.40	1.14 (0.84-1.53)
Dfov [‡]	-0.123 (0.081)	2.31	0.13	0.88 (0.75-1.04)
Ddisk [‡]	-0.111 (0.091)	1.49	0.22	0.90 (0.75-1.07)
Dose to apex [‡]	-0.114 (0.115)	0.99	0.32	0.89 (0.71-1.12)
Dose to sclera [‡]	0.034 (0.125)	0.08	0.78	1.04 (0.81-1.32)
Eccentricity [§]				
Parallel	1.223 (0.541)	5.11	0.024	3.40 (1.18-9.80)
Not covered	0.797 (0.586)	1.85	0.17	2.22 (0.70-7.00)
Positioning	1.035 (0.506)	4.16	0.041	2.81 (1.04-7.59)
<i>Bivariable analysis[¶]</i>				
Plaque [*]	0.710 (0.454)	2.44	0.12	2.03 (0.83-4.96)
Positioning	1.000 (0.507)	3.90	0.048	2.72 (1.01-7.35)

CI, confidence interval; Dfov, distance to foveola; Ddisk, distance to optic disk; LBD, largest basal diameter; SE standard error

^{*} Categories: 0 = 10-mm plaque; 1 = 15-mm plaque

[†] Continuous variable (mm)

[‡] Continuous variable (10 Gy for apex, 100 Gy for sclera)

[§] Remodeling; Categories: 0 = Covered; 1 = Parallel; 2 = Not covered

^{||} Remodeling; Categories: 0 = Covered; 1 = Parallel or not covered

[¶] Final model

Table 9. Cox proportional Hazards Regression of Time to Lost Vision of 20/65 or Worse (Low Vision) and 20/400 (Blindness) in the Tumor Eye of 164 Patients with a Small Choroidal Melanoma of whom 76 underwent brachytherapy with 10-mm and 88 with 15-mm Ruthenium Plaque

Variable	Low Vision				Blindness			
	Coefficient (SE)	Wald χ^2	P	Hazard Ratio (95% CI)	Coefficient (SE)	Wald χ^2	P	Hazard Ratio (95% CI)
<i>Univariable analysis</i>								
Plaque*	0.337 (0.308)	1.20	0.27	1.40 (0.77-2.56)	-0.007 (0.437)	0.98	0.99	0.99 (0.42-2.34)
Thickness [†]	0.266 (0.151)	3.12	0.077	1.31 (0.97-1.75)	0.422 (0.189)	4.99	0.025	1.53 (1.05-2.21)
LBD [‡]	-0.0169 (0.110)	0.02	0.88	0.98 (0.79-1.22)	-0.029 (0.157)	0.03	0.86	0.97 (0.71-1.32)
Dfov [†]	-0.428 (0.093)	21.01	<0.001	0.65 (0.54-0.78)	-0.380 (0.131)	8.36	0.004	0.68 (0.53-0.88)
BCVA baseline [‡]	-1.836 (0.536)	11.74	0.001	0.16 (0.06-0.46)	-1.207 (0.595)	4.11	0.043	0.30 (0.09-0.96)
Positioning [§]	0.038 (0.318)	0.01	0.91	1.04 (0.56-1.94)	0.315 (0.470)	0.45	0.50	1.37 (0.55-3.44)
<i>Bivariable analysis</i>								
Model 1	-2 log likelihood = -401.61				-2 log likelihood = -190.43			
Plaque*	0.166 (0.336)	0.24	0.62	1.18 (0.61-2.28)	-0.399 (0.488)	0.67	0.41	0.67 (0.26-1.75)
Thickness [†]	0.233 (0.16)	1.97	0.16	1.26 (0.91-1.75)	0.494 (0.209)	5.58	0.018	1.64 (1.09-2.47)
Model 2	-2 log likelihood = -402.33				-2 log likelihood = -195.35			
Plaque*	0.496 (0.355)	1.95	0.16	1.64 (0.82-3.30)	0.052 (0.509)	0.01	0.92	1.05 (0.39-2.86)
LBD [‡]	-0.108 (0.123)	0.77	0.38	0.90 (0.70-1.14)	-0.038 (0.183)	0.04	0.83	0.96 (0.67-1.38)
Model 3	-2 log likelihood = -367.46				-2 log likelihood = -182.58			
Plaque*	0.582 (0.310)	3.54	0.060	1.79 (0.98-3.29)	0.188 (0.439)	0.18	0.67	1.21 (0.51-2.85)
Dfov [†]	-0.448 (0.095)	22.08	<0.001	0.64 (0.53-0.77)	-0.385 (0.132)	8.50	0.004	0.68 (0.53-0.88)
Model 4	-2 log likelihood = -394.74				-2 log likelihood = -192.37			
Plaque*	0.330 (0.308)	1.15	0.28	1.39 (0.76-2.54)	-0.021 (0.438)	0.01	0.96	0.98 (0.41-2.31)
BCVA baseline [‡]	-1.864 (0.548)	11.55	0.001	0.16 (0.05-0.45)	-1.208 (0.596)	4.11	0.043	0.30 (0.09-0.96)
<i>Trivariable analysis</i>								
Model 5	-2 log likelihood = -366.00				-2 log likelihood = -182.0			
Plaque*	0.551 (0.310)	3.15	0.076	1.73 (0.94-3.19)	0.180 (0.439)	0.17	0.68	1.20 (0.51-2.83)
Dfov [†]	-0.416 (0.098)	18.10	<0.001	0.66 (0.54-0.80)	-0.361 (0.135)	7.13	0.008	0.70 (0.53-0.91)
BCVA baseline [‡]	-0.943 (0.753)	1.57	0.211	0.39 (0.09-1.71)	-0.587 (0.710)	0.68	0.41	0.56 (0.14-2.23)
Model 6	-2 log likelihood = -364.66				-2 log likelihood = -176.00 [¶]			
Plaque*	0.360 (0.341)	1.13	0.29	1.44 (0.74-2.80)	-0.190 (0.474)	0.16	0.69	0.83 (0.33-2.09)
Dfov [†]	-0.458 (0.096)	22.64	<0.001	0.63 (0.52-0.76)	-0.438 (0.143)	9.35	0.002	0.65 (0.49-0.85)
Thickness [†]	0.316 (0.186)	2.89	0.089	1.37 (0.95-1.98)	0.619 (0.232)	7.14	0.008	1.86 (1.18-2.92)

CI, confidence interval; Dfov, distance to foveola; Ddisk, distance to optic disk; LBD, largest basal diameter; SE, standard error; BCVA, best corrected visual acuity

* Categories: 0 = 10-mm plaque; 1 = 15-mm plaque; [†] Continuous variable (mm); [‡] Continuous variable (0.1 – logMAR units)

[§] Remodeling; Categories: 0 = Covered; 1 = Parallel or not covered, ^{||} Final model for development of low vision, [¶] Final model for development of blindness

Comparison of outcomes after ruthenium brachytherapy with the 10-mm and 15-mm plaque supports
use of the 10-mm plaque for choroidal melanomas <10 mm in largest basal diameter based on
multivariable analysis of complications and vision.