

Physics Contribution

Dosimetric Benefit of a New Ophthalmic Radiation Plaque

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Summary

Uveal melanoma is most often treated with Collaborative Ocular Melanoma Study (COMS) I-125 brachytherapy plaques with excellent disease control, albeit with radiation-induced visual loss. For 100 uveal melanoma patients, a dosimetric study between COMS plaques and a new ophthalmic plaque, EP917, compared radiation dosage to vision critical structures for each plaque. EP917 delivered significantly less radiation to certain visual structures while maintaining adequate tumor coverage. Translation to clinical visual improvement with the new plaque remains to be proved.

Purpose: To determine whether the computed dosimetry of a new ophthalmic plaque, EP917, when compared with the standard Collaborative Ocular Melanoma Study (COMS) plaques, could reduce radiation exposure to vision critical structures of the eye.

Methods and Materials: One hundred consecutive patients with uveal melanoma treated with COMS radiation plaques between 2007 and 2010 were included in this study. These treatment plans were generated with the use of Bebig Plaque Simulator treatment-planning software, both for COMS plaques and for EP917 plaques using I-125. Dose distributions were calculated for a prescription of 85 Gy to the tumor apex. Doses to the optic disc, opposite retina, lens, and macula were obtained, and differences between the 2 groups were analyzed by standard parametric methods.

Results: When compared with the COMS plaques, the EP917 plaques used fewer radiation seeds by an average difference of 1.94 ($P < .001$; 95% confidence interval [CI], -2.8 to -1.06) and required less total strength of radiation sources by an average of 17.74 U (air kerma units) ($P < .001$; 95% CI, -20.16 to -15.32). The total radiation doses delivered to the optic disc, opposite retina, and macula were significantly less by 4.57 Gy, 0.50 Gy, and 11.18 Gy, respectively, with the EP917 plaques vs the COMS plaques.

Conclusion: EP917 plaques deliver less overall radiation exposure to critical vision structures than COMS treatment plaques while still delivering the same total therapeutic dose to the tumor. © 2012 Elsevier Inc.

Keywords: Uveal melanoma, Episcleral plaque, Dosimetry, Ophthalmic, Brachytherapy

Introduction

Uveal melanoma is most frequently treated with brachytherapy by the use of custom-designed episcleral plaques (1). Since the

Collaborative Ocular Melanoma Study (COMS) was initiated in 1985 (2-4), I-125 has been the most frequently used radionuclide in the United States, whereas ruthenium-106 is preferred in Europe (5). Excellent primary tumor control rates ranging from 90%-95% have been reported with I-125 episcleral plaque

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radiotherapy. However, moderate loss of vision secondary to radiation-related complications like retinopathy and optic neuropathy is observed in a large proportion of cases (6). In the COMS randomized trial of I-125 brachytherapy for medium-sized choroidal melanoma, loss of 6 or more lines of visual acuity from the pretreatment level occurred in 49% of eyes after 3 years (7).

The complications of radiation retinopathy and optic neuropathy are essentially untreatable over the long term, although short-term benefit with laser photocoagulation, the use of intravitreal triamcinolone acetate, or anti-vascular endothelial growth factor treatment in nonrandomized case series has been reported (8). Therefore, it has become increasingly more important to find ways to avoid radiation retinopathy and optic neuropathy. The total dose of radiation to critical ocular structures such as the macula and optic disc is the major modifiable risk factor for radiation retinopathy and optic neuropathy after I-125 plaque radiation therapy (7, 9-12). The approaches available to reduce collateral radiation dose include prescription of less than a conventional therapeutic dose of 85 Gy to the tumor apex (13), the use of alternative radionuclides such as strontium-90, ruthenium-106, and palladium-103 (14), or attenuation of radiation using silicon endotamponade (15).

Another approach would be to improve on existing COMS plaque designs (16, 17). In the COMS plaque, I-125 seeds are loaded in a Silastic carrier that is placed within gold casing in such a manner that the seeds are 1 mm away from the sclera, allowing for a more homogeneous dose distribution (Fig 1A) (3). By designing plaques wherein the seeds are glued into the shallow grooves of the gold, the need for a carrier disappears, and the I-125 seeds can now be placed in close proximity to the sclera (Eye Physics, LLC, Los Alamitos, CA) (Fig 1B) (18). The collimated field from each seed is designed to overlap just below the base of the tumor, which also provides a homogenous distribution of the radiation (16). Such a plaque has a theoretical advantage of reduced lateral dose as confirmed by thermoluminescent dosimeter and radiochromic film studies (16).

We performed a study of 100 consecutive cases of posterior uveal melanoma to determine whether the dosimetry of a new ophthalmic plaque (EP917) when compared with the COMS plaques would reduce radiation exposure to vision critical structures of the eye.

Methods and Materials

A series of 100 consecutive patients treated at the Department of Ophthalmic Oncology, Cole Eye Institute, Cleveland Clinic, between the years 2007 and 2010, with a clinical diagnosis of posterior uveal melanoma based on ophthalmoscopy, ultrasonographic features, and angiographic studies, was used in this study. The tumors ranged in height from 2.42 mm-14.00 mm, representing the full spectrum of small, medium, and large melanomas according to COMS criteria. Each patient was planned with Plaque Simulator (Eckert & Ziegler BEBIG GmbH, Berlin, Germany) and treated with COMS radiation plaques (Trachsel Dental Studio, Rochester, MN). Each plaque was chosen to be the smallest one that provided adequate target coverage (V100 >98%). Later, these same cases were replanned with the EP917 plaque (Eye Physics, LLC, Los Alamitos, CA). Each new plan involved treatment planning and dosimetry based on retinal diagrams from the original COMS plans. No patient was treated with the EP917 plaque. The location of each tumor was expressed as the distance in millimeters of the nearest tumor margin to the center of the optic disc and center of the macula.

In all cases, each type of plaque was centered on the tumor base. The COMS plaques were fully loaded with I-125 seeds, whereas the EP917 plaques were loaded with only enough seeds to ensure that the V100 exceeded 98%. In each plaque, the seeds were of equal source strength adjusted to deliver a total therapeutic dose of 85 Gy to the tumor apex over the course of 72 hours. Again, the treatment planning system used was Plaque Simulator. Dosimetric verification of this system has been

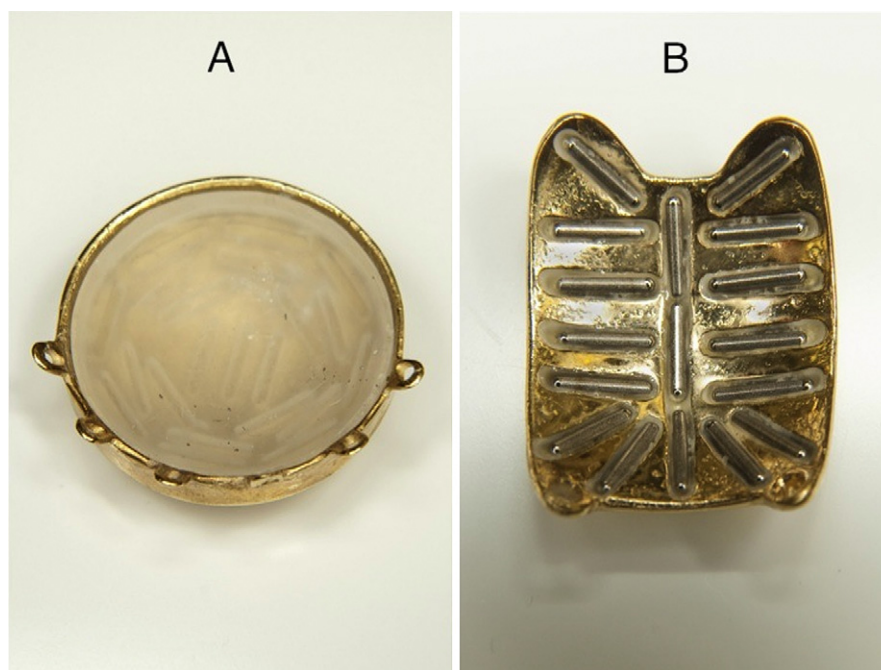


Figure 1. Inner views of the Collaborative Ocular Melanoma Study (COMS) plaque (A) and the Eye Physics (EP)917 plaque (B).

Table 1 Summary of radiation data: COMS and EP917 plaques

| Plaque | Factor | Mean | SD | Minimum | Median | Maximum |
|--------|------------------------------|--------|--------|---------|--------|---------|
| COMS | Number of seeds | 13.96 | 5.43 | 7.00 | 13.00 | 24.00 |
| | Total activity (U) | 79.54 | 57.38 | 32.40 | 59.56 | 373.00 |
| | Dose to optic disc (Gy) | 31.85 | 25.69 | 5.05 | 27.56 | 206.10 |
| | Dose to opposite retina (Gy) | 6.19 | 4.69 | 2.20 | 4.66 | 28.10 |
| | Dose to lens (Gy) | 17.29 | 19.06 | 3.40 | 9.71 | 98.48 |
| | Dose to macula (Gy) | 57.54 | 44.52 | 5.63 | 50.56 | 238.20 |
| | Dose to sclera (Gy) | 229.35 | 117.90 | 118.20 | 189.75 | 820.20 |
| EP917 | Number of seeds | 12.03 | 3.96 | 2.00 | 13.00 | 17.00 |
| | Total activity (U) | 61.80 | 46.93 | 20.83 | 44.75 | 298.00 |
| | Dose to optic disc (Gy) | 27.28 | 22.50 | 4.72 | 22.20 | 162.50 |
| | Dose to opposite retina (Gy) | 5.69 | 4.35 | 1.80 | 4.10 | 27.27 |
| | Dose to lens (Gy) | 17.07 | 19.75 | 2.70 | 9.48 | 110.70 |
| | Dose to macula (Gy) | 46.36 | 41.06 | 5.13 | 37.05 | 233.00 |
| | Dose to sclera (Gy) | 220.01 | 148.76 | 104.00 | 163.65 | 931.90 |

Abbreviations: COMS = Collaborative Ocular Melanoma Study; EP = Eye Physics; SD = standard deviation.

published by Knutsen et al (19). The computations for this study incorporated the nonhomogeneity corrections for the Silastic carrier and the gold alloy backing.

Next, the number of seeds, total required radiation source strength, and total doses to critical structures of the eyes were compared head to head between the original COMS plaque and the EP917 plaque. The differences were described by means, standard deviations (SD), and 95% confidence intervals (CI) and were compared by dependent *t* tests.

Differences in radiation doses to the critical structure between COMS plaque and EP917 plaque were calculated as EP917-COMS plaque, so that a negative measure reflects less radiation dose with EP917 plaque. Also, the relationship between the dose differences with COMS vs EP917 and the distance of the tumors from critical vision structures was assessed by a Pearson correlation test. Normality of the differences between the COMS and EP917 data was assessed empirically before testing, and non-parametric methods (Wilcoxon signed ranked tests and Spearman correlations) were used as a sensitivity analysis. Additionally, a McNemar test was used to evaluate the ability to keep macula doses under thresholds of 30 Gy, 40 Gy, or 50 Gy. Statistical analysis was performed with R software (version 2.8; Vienna, Austria), and all statistical tests used a significance level of .05.

Results

The 100 consecutive patients had a median age of 63 years (range, 26-89 years) with uveal melanoma treated with COMS plaques

and then replanned for treatment with the EP917 plaques (Table 1). When compared with the COMS plaque, the mean number of radiation seeds used in the EP917 plaque was fewer by 1.94 ($P<.001$; 95% CI; -2.8 to -1.06), and the total strength of radiation sources was also reduced by 17.74 U ($P<.001$; 95% CI, -20.16 to -15.32).

The mean radiation dose (Gy) delivered to the optic disc, opposite retina, and macula was less by 4.57 ($P<.001$; 95% CI, -6.91 to -2.23), 0.50 ($P<.001$; 95% CI, -0.72 to -0.28), and 11.18 ($P<.001$; 95% CI, -14.58 to -7.78), respectively, for the EP917 plaque vs the COMS (Table 2). The mean of total Gy delivered to the lens was less by 0.23 Gy, although this was not statistically significant ($P=.48$).

The correlation between distance of tumor from center of macula, and difference in dose delivered between EP917 and COMS, was 0.44 ($P<.001$; 95% CI, 0.26-0.58). Statistically significant positive associations were observed between the distance and the difference in the total radiation doses to the macula. For tumors near the macula, the reduction in dose with the EP917 plaque was greater. For tumors farther away from the macula (8 mm or more), the difference in the dose was very close to zero. Correlation between distance of tumor from optic disc, and difference in dose delivered to optic disc between EP917 and COMS, was 0.06 not statistically significant ($P=.54$).

For threshold doses to the macula, both methods delivered ≤ 40 Gy in 44 cases (44%) and >40 Gy for 46 cases (46%); for the remaining 10 cases, the COMS delivered a dose >40 Gy, and EP917 delivered a dose ≤ 40 Gy ($P=.004$). There were no cases wherein a COMS plaque delivered ≤ 40 Gy and the EP917 plaque

Table 2 Difference in radiation dose (Gy) delivered to various critical structures (calculated as EP917 plaque dose minus COMS plaque dose)

| Structure | <i>n</i> | Mean | SD | Lower 95% CI | Upper 95% CI | <i>P</i> value |
|-----------------|----------|--------|-------|--------------|--------------|----------------|
| Optic disc | 100 | -4.57 | 11.81 | -6.91 | -2.23 | <.001 |
| Opposite retina | 100 | -0.50 | 1.13 | -0.72 | -0.28 | <.001 |
| Lens | 100 | -0.23 | 3.23 | -0.87 | 0.41 | .48 |
| Macula | 100 | -11.18 | 17.16 | -14.58 | -7.78 | <.001 |
| Sclera | 100 | -9.34 | 44.67 | -18.20 | -0.48 | .039 |

Abbreviations: COMS = Collaborative Ocular Melanoma Study; EP = Eye Physics; SD = standard deviation; CI = confidence interval; (-) = COMS plaque dose is greater than EP917 plaque dose; (+) = EP917 plaque dose is greater than COMS ¹²⁵Iodine plaque dose.

Table 3 Macular radiation dose: COMS vs EP917

| Dose (Gy) | | EP917: No | EP917: Yes | P value |
|-----------|----------------------------|-----------|------------|---------|
| >30 | COMS ¹²⁵ I: No | 35 | 1 | .027 |
| | COMS ¹²⁵ I: Yes | 9 | 55 | |
| >40 | COMS ¹²⁵ I: No | 44 | 0 | .004 |
| | COMS ¹²⁵ I: Yes | 10 | 46 | |
| >50 | COMS ¹²⁵ I: No | 50 | 0 | <.001 |
| | COMS ¹²⁵ I: Yes | 13 | 37 | |

Abbreviations: COMS = Collaborative Ocular Melanoma Study; EP = Eye Physics.

delivered >40 Gy. Similar observations favoring the EP 917 plaque were made for threshold values >30 Gy and >50 Gy (Table 3).

Analysis of radiation dose to the optic disc in this study revealed that in 17 cases the COMS delivered a dose >30 Gy, and EP917 delivered a dose ≤30 Gy ($P=.001$). Both plaques delivered ≤30 Gy in 57 cases (57%) and >30 Gy for 26 cases (26%). There were no cases wherein COMS delivered ≤30 Gy and EP917 plaque >30 Gy. Similar observations favoring the EP 917 plaque were made for threshold values >30 Gy.

Discussion

The total dose of radiation to critical ocular structures such as the macula and the optic disc is the major modifiable risk factor for radiation retinopathy and optic neuropathy after I-125 plaque radiation therapy (7, 9–12). Collimated I-125 plaques have been designed to offer conformal therapy by providing greater dose homogeneity within the tumor and reducing the radiation to uninvolved adjacent structures (16).

Our data suggest that in a head-to-head dosimetric comparison of the same radioisotope, I-125, EP917 has superior dose sparing to critical vision structures of the eye vs the COMS. Specifically, 2 of the most vital vision structures, the macula and the optic disc, received significantly less radiation dosage with the EP917 vs

the COMS (Fig 2). Our findings are similar to a previous study wherein collimating plaques were simulated for large melanomas (17).

Studies based on treatment with proton beam radiation have indicated that the risk of maculopathy increases linearly up to 40 Gy before plateauing (20). Analysis of radiation dose to the macula in our study indicates that in several cases, the COMS plaque delivered a dose >40 Gy and EP917 delivered a dose of ≤40 Gy, but not vice versa. These findings indicate the possibility for a lower likelihood of radiation maculopathy with the use of EP917 plaques. Regarding radiation optic neuropathy, the risk is negligible below 30 Gy, with a gradual rise to 100% risk at 70 Gy (20). Analysis of radiation dose to the optic disc in our study indicates that in a large number of cases, the COMS plaque delivered a dose >30 Gy and EP917 delivered a dose ≤30 Gy. These significant findings indicate the possibility for lower likelihood of radiation optic neuropathy with EP917 plaques.

Given that the risks of radiation retinopathy and optic neuropathy are dose dependent and both entities are essentially untreatable, one way to achieve superior visual outcomes after brachytherapy for uveal melanoma would be to reduce radiation dose to the vision critical structures. Our data, based on analysis of 100 consecutive cases, suggest that the EP917 plaque offers theoretical advantage over the COMS plaque. However, benefit from a clinical outcome standpoint has not yet been demonstrated.

One of the limitations of our study is that we used only one size of EP917 plaque for simulation because it is the only collimated Eye Physics plaque with verified dosimetry. We compared one size of EP917 plaque with various sized, notched/not-notched COMS plaques that had all been dosimetrically verified. The COMS plaque may still be superior for tumors that are in proximity to the optic disc, because of the availability of “notched” COMS plaques. However, in our study, there was no selection bias to the shape, size, or location of each tumor because we randomly selected 100 consecutive cases to estimate benefit in the clinical setting. Regardless of these factors, less dose was delivered to vision critical structures with the EP917 plaque.

Additionally, our data suggest that, on average, fewer sources and reduced total source strength are associated with use of the

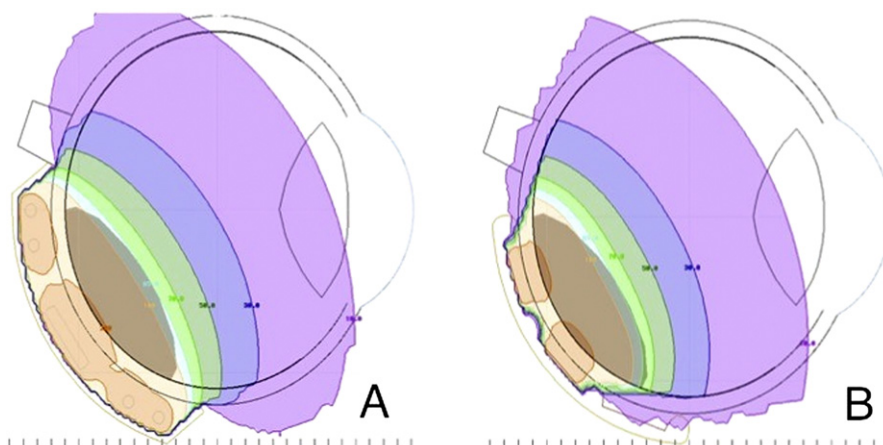


Figure 2. Two-dimensional volumetric diagram with prescription isodose lines. The Collaborative Ocular Melanoma Study (COMS) 18-mm plaque (A) has 21 seeds. The EyePhysics 16- × 14-mm plaque (B) has 17 slots (each slot measures 1.0 × 5.0 × 0.8 mm), but only 14 are loaded, wherein all seeds are of the same strength in units of air kerma (U). For both plaque diagrams, isodose lines are in Gray units. Treatment dose is 85 Gy to tumor apex (light blue) delivered in 72 hours.

EP917 plaque. This has the potential of reducing costs because individual seed pricing depends somewhat on source strength.

In summary, our data indicate that the commercially available EP917 plaque (which has still not received approval from the US Food and Drug Administration) has distinct dosimetric advantages over COMS plaques. For the full range of tumor sizes treated with plaque radiation therapy, the use of EP917 plaques is expected to reduce costs. The EP917 plaques provide for a conformal distribution of radiation with lower exposure to critical ocular structures. Whether these dosimetric benefits translate into clinically significant improved visual outcomes after brachytherapy of posterior uveal melanoma remains to be proved.

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