A Reanalysis of the Collaborative Ocular Melanoma Study
Medium Tumor Trial Eye Plaque Dosimetry

Amanda L. Krintz M.S.¹, William F. Hanson, Ph.D.,
Geoffrey S. Ibbott, Ph.D., and David S. Followill, Ph.D.

Department of Radiation Physics
The University of Texas M. D. Anderson Cancer Center
Houston, Texas

¹Current Address:
Hulston Cancer Center
Springfield, MO

Corresponding Author:
David S. Followill, Ph.D.
M.D. Anderson Cancer Center
Department of Radiation Physics, Box 547
1515 Holcombe Blvd.
Houston, Texas 77030
(713) 745-8989
(713) 794-1364 fax
E-mail: rpc@radonc.mdacc.tmc.edu

Running Title
COMS Eye Plaque Dosimetry Reanalysis
Abstract

Purpose: To recalculate the radiation doses delivered to critical structures of the eye lens, tumor apex, 5 mm point, optic disc, and macula for patients treated with eye plaque radiotherapy on the Collaborative Ocular Melanoma Study (COMS) Medium Tumor Trial, using updated dosimetric data.

Methods: Using the Plaque Simulator planning system (BEBIG, Berlin, Germany), doses were recalculated for a sampling of COMS patients for each plaque size. Dosimetry parameters incorporated into the recalculation were line source approximation, a 90% silastic transmission factor, and a 0% gold transmission factor. Generic solutions were generated from the dose recalculations for each plaque size and critical structure combination. Doses for the remainder of the patient population were recalculated using the generic solutions and compared with the originally reported COMS doses.

Results: Doses to all critical structures were reduced 7-21% depending on the plaque size and critical structure combination. The closer the structure was to the plaque, the greater the dose reduction. Incorporation of the silastic transmission factor accounted for a large part of the dose reduction.

Conclusions: Incorporating anisotropy, line source approximation, and silastic and gold shield attenuation into dose recalculations resulted in a significant and consistent reduction of doses to critical structures of the eyes.

Choroidal melanoma, Plaque radiotherapy, Radiation dosimetry.

INTRODUCTION
Choroidal melanoma is the most common malignant ocular tumor in adults (1). Standard treatment since the early 1900s has been enucleation of the involved eye (2). However, beginning in the 1930s radiation therapy was proposed as a way to save the eye and possibly some vision. While various nuclides have been tried throughout the years, the current choice for eye plaque therapy is $^{125}\text{I}$. Iodine-125 is a low energy photon emitter and therefore less of a radiation hazard to personnel and other normal tissues in the patient’s body (3-8).

Despite this history, no decision had ever been reached as to which mode of therapy, enucleation or eye plaque radiotherapy, provides better control and survival. So, in 1986, the Collaborative Ocular Melanoma Study (COMS) Group initiated a randomized multicenter clinical trial to compare the efficacy of radiotherapy versus enucleation in medium-sized tumors (i.e., unilateral tumors ranging in height from 2.5 mm to 10 mm and no more than 16 mm in diameter).(1)

Between 1987 and 1998, the trial accrued 1317 patients, 657 of whom were randomized to the radiotherapy arm. Patients in the radiotherapy arm were treated with an eye plaque of COMS Group design, which was available in 5 sizes (12, 14, 16, 18, and 20 mm diameter). In each case, the plaque used had to cover the tumor and a 2-3 mm margin around its base, unless the tumor was adjacent to the optic nerve, in which case exceptions could be made. The initial prescribed dose, which was administered to the apex of the tumor or to within 5 mm of the interior surface of the sclera (the 5 mm point), was 100 Gy. In 1996, this was changed to 85 Gy when the dosimetry formulism of American Association of Physicists in Medicine (AAPM) Task Group 43 (9) was applied.

The original COMS dosimetry calculations made several assumptions that allowed for more consistent prescription of doses by recognizing larger uncertainties in the doses delivered to critical normal tissues. The assumptions were that the $^{125}\text{I}$ seeds were point sources and that no corrections
would be made for anisotropy, side attenuation or backscatter due to the gold shield, or attenuation due to the silastic insert.

Following completion of the COMS trial, patient follow-up continued so that, at present, the majority of the patients have been followed for at least 5 years. Analysis of the follow-up data by personnel in the COMS Coordinating Center revealed no statistical difference in survival between the two treatment arms and very little correlation between the dose to critical structures (e.g., macula and optic disc) and visual acuity outcome (10).

The poor correlation between dose and visual acuity outcome has raised questions, however, about the dosimetry calculations used in the COMS trial, especially since methods for calculating dosimetry have improved immensely since the COMS trial began in 1986. Therefore, the aim of the present stay to recalculate the radiation doses received by the patients randomized to the radiotherapy arm of the COMS Medium Tumor Trial using the most up-to-date dosimetric methods and techniques.

**MATERIALS AND METHODS**

A total of 657 patients in the COMS Medium Tumor Trial were treated with COMS Group designed eye plaques. Of these, 57 patients were excluded from the present study because they were treated with nonstandard plaques. The remaining 600 patients were included for analysis in the present study.

The original doses to the tumor and critical structures were calculated assuming a point source, no anistropy, and no attenuation due to gold backing or silastic insert of the plaque. An eye plaque radiotherapy planning system (Plaque Simulator [PS] (© BEBIG GmbH, Berlin, Germany) was used to recalculate the tumor and critical structure doses (11). This planning system’s dose distribution accuracy
had been previously verified using radiochromic film (12), diodes (13), and TLD (14). The PS system incorporates the most up-to-date dosimetry data including line source approximations, anisotropy, silastic attenuation and gold shield attenuation. In addition to allowing more accurate dose calculations, the PS system also allows the user to vary the rotation of the plaque in order to determine the change in dose to critical structures as a function of plaque rotation.

Because of the large number of recalculations required, it was decided that a generic solution based on a sampling of patients would be generated first and then used to recalculate the doses for our study population. The first step in the recalculation process was to divide the patients into 5 subgroups by plaque size (12, 14, 16, 18, and 20 mm). The second step was to further subdivide the patients into subgroups as follows: all plaques loaded with Amersham, model 6711 radioactive seeds (Amersham, Arlington Heights, IL), all plaques loaded with Amersham model 6702 radioactive seeds (Amersham, Arlington Heights, IL), 12 mm plaques missing any seeds, 14 to 20 mm plaques missing more than 3 seeds, and plaques with a scleral offset. These further divisions were necessary because (a) the missing seeds caused changes in dose that had to be considered, (b) the model 6702 seeds had different dosimetric properties than the model 6711 seeds, and (c) use of the scleral offset meant that an extra 1 mm of muscle attenuation had to be accounted for in calculating the dose.

Once the patients were divided into the above mentioned categories, the largest category, (i.e., all patients whose plaques were loaded with model 6711 seeds and were missing no more than 3 seeds [n = 481]), was labeled the generic population. From the generic population, a set of patients in each plaque size group was randomly chosen to have their data manually entered into the PS system for dose recalculation. The critical structures for which the doses were recalculated were the macula, optic disc, lens, tumor apex, and 5 mm point. These patients were designated the training set.
For each member of the training set, a quantity \( X \) was calculated as follows:

\[
X = \frac{\text{No. seeds} \times \text{AirKermaStrength} \times \text{Duration}}{\text{Length}^2}
\]

This equation incorporates all of the basic factors used in any brachytherapy dose calculation, including arc length from the tumor center to the point of interest along the inner sclera for the macula and optic disc and chord length for the tumor apex, lens, and 5 mm point. The values used in the above equation were provided in a COMS patient database that made it very simple to calculate \( X \) for all 481 patients in the generic population. The training set patients whose doses were recalculated using the PS system were first selected randomly and then a few more were chosen in order to cover the entire range of \( X \) values for the generic population and generate the best possible generic solution. The uncertainty in the delivered dose due to plaque rotation was accounted for by basing the generic solution on the average dose delivered to a given structure for plaque rotations from 0° to 360° in 10° increments. The average dose was then plotted against the \( X \) values.

To calculate the dose for any value of \( X \) for each combination of plaque size and critical structure, a generic solution was determined from the training set recalculations. This generic solution was then used to recalculate the doses for the rest of the generic population, based on the \( X \) value for each patient. To verify the generic solution, doses were recalculated manually for a set of four additional patients in each plaque size group.

Doses for the 119 patients who did not fit into the generic population were all recalculated manually using the PS system. In brief, each patient’s chart was reviewed for the specifics of plaque treatment, and the data were entered into the PS system.
The recalculated (PS) radiation doses were then compared with the originally reported COMS doses by establishing the ratio of the recalculated doses to the originally reported doses (PS/COMS) and reporting the differences as percentages. The new recalculated doses accounted for anisotropy, plaque rotation uncertainty, and silastic and gold attenuation.

RESULTS AND DISCUSSION

Twenty-five generic solutions were generated for recalculating the dose to the tumor apex, 5 mm point, sclera, macula, and optic disc for the 481 patients in the generic population. A generic solution was generated for each plaque size and critical structure combination. All 25 generic solutions are listed in Appendix I. Representative generic solutions for the 14 mm plaque are shown in Figures 1a-e. The equation for each generic solution and the $R^2$ value describing its goodness of fit are shown on the graph along with the data points in the training set and validation set. The generic solutions took the form of linear, nth-order polynomials and natural log function equations (Table 1). The generic solutions all fit within ±6% of the training set points and validation set points, with the majority fitting within ±4%.

Our comparison of the originally reported COMS doses (TG-43 point source) with the recalculated (PS) doses is summarized in Table 2, which shows the ratios of average recalculated doses to originally reported doses (±1 SD) and the range (for the central 95% of the data points) of ratios for each plaque size and critical structure combination. These ratios ranged from 79% to 93%, with the mean change primarily reflecting the 10% reduction due to attenuation by the silastic insert. Since COMS doses used in the comparison were those reported by the participating institutions and verified by the Radiological Physics Center (RPC) to within ±10% for the prescription point and ±15% for
critical structures, some of the standard deviation may be due to differences between the institutions' reported dose calculations and the RPC’s calculated doses. It is important to note, however, that the data in Table 2 is just a summary and that a simple average ratio is not a valid correction factor for a specific plaque size and critical structure combination. As can be seen by the ranges displayed in Table 2, the actual PS/COMS ratios varied significantly throughout the generic population. These values were also averaged over various angles of plaque rotation, so that there is additional uncertainty (± 5–20%) due to plaque rotation 12 mm and 20 mm plaque sizes (Figs. 2a and 2b), respectively.

The generic solutions we generated provide a method for checking the calculated doses for the five mentioned critical structures for each of the five COMS plaque sizes. One must remember, however, that any dose calculated from one of these generic solution incorporates all of the possible dosimetry corrections that were not implemented in the COMS Medium Tumor Trial. In addition, if an institution clinically prescribes their plaque doses according to the COMS prescription, i.e., 85 Gy to the tumor apex or 5 mm point, then the generic solutions will yield doses of 10-13% less along the central axis due to the dosimetry considerations used here.

Figures 3 and 4 provide alternate ways of displaying our comparison between the originally reported COMS doses and the recalculated (PS) doses. Figure 3 shows the relationship between the recalculated doses and the originally reported COMS doses for the delivery to the macula from the 20 mm plaque and is representative of the relationship between the recalculated doses and the originally reported doses for all other combinations of plaque size and critical structure. In the vast majority of cases, recalculated doses shown are less than the reported COMS doses and the amount by which they differ varies with dose. For those critical structures receiving larger doses, which implies a location closer to the center of the plaque, the change on recalculation was larger than for those critical structures...
that were farther away from the tumor. This makes sense since the amount of change caused by anisotropy, silastic and gold shield attenuation, and averaging of plaque rotations was greater for points closer to the tumor.

Figure 4 is a histogram of the PS/COMS ratio for the dose to the macula from the 20 mm plaque and is representative of the histograms of PS/COMS dose ratios for all other combinations of plaque size and critical structure. In all cases, the distribution of PS/COMS dose ratios shown skewed toward values less than 0.9.

As mentioned previously, only the central 95% of the data were included in our comparisons (Table 2, Fig. 3, and Fig. 4) because some data that could not be reviewed retrospectively (5%) skewed the results. Ratios were considered non-renewable for one of three reasons: (a) there were unresolved discrepancies between an institution’s reported COMS dose and the RPC’s calculated dose, (b) an incomplete data set had been stored in the COMS database, (c) structures that received a very low dose had a PS/COMS dose ratio that was well over 1 or less than 0.5 but represented a clinically insignificant change in dose.

In conclusion, using updated dosimetry parameters and taking into account the physical characteristics of the COMS eye plaque, we recalculated the average COMS dose to five critical structures of the eye and arrived at 7 -21% lower doses. The amount of reduction was partially dependent upon the location of the critical structure with respect to the plaque itself. Moreover, using the PS treatment planning system we generated a generic solutions for all critical structure and plaque size combinations in our study in order to quickly recalculate the dose for the entire patient population. These generic solutions now provide a method for checking the calculated doses for critical structures for all five COMS plaque sizes. The amount of reduction in the dose to critical structures could be
clinically significant, so future eye plaque dosimetry should be performed using the most up-to-date parameters available.

Acknowledgements

This work was supported by Public Health Service Grant EY 06266, awarded by the National Eye Institute, Department of Health and Human Services.
REFERENCES


FIGURE LEGENDS

Fig. Ia. Generic solution for dose to (a) 5 mm point, (b) tumor apex, (c) lens, (d) optic disc, and (e) macula for 14 mm plaque. The individual doses calculated for the training set and validation set are included. The function fit and its $R^2$ value are listed.

Fig. II. Doses for each plaque rotation calculated along the inner sclera of the eye for (a) 14 mm plaque and (b) 20 mm plaque as the plaque is rotated in 15° degree increments from 0° to 180°.

Fig. III. Scatter plot of recalculated (PS) doses vs. reported COMS doses to the macula for patients treated with the 20 mm plaque. The line represents equality.

Fig. IV. Histogram showing the distribution of the ratios of recalculated (PS) doses to reported COMS doses to the macula for patients treated with the 20 mm plaque.
Figure Ia

\[ y = 0.2938x + 1.2257 \]

\[ R^2 = 0.9981 \]

Dose (Gy) vs. \( x \) values (U/\( hr/mm^2 \))

- **Generic Solution**
- **Training Set**
- **Validation Set**
Figure Ib

The graph shows the relationship between dose (Dose in Gy) and the product of X values (U*hr/mm^2) on the Y-axis. The data points are categorized into three sets: Training Set (squares), Validation Set (triangles), and the Generic Solution represented by a solid line.

The equation of the line is given by:

\[ y = 7.71341 \times 10^{-2}x + 6.08133 \times 10^1 \]

with the coefficient of determination \( R^2 = 0.9656 \).
$y = 5.883071 \times 10^{-1} x - 1.303826 \times 10^{0}$

$R^2 = 0.9945$

**Figure Ic**
\[ y = -5.77507 \times 10^{-6}x^3 + 2.17836 \times 10^{-3}x^2 + 5.74554 \times 10^{-1}x + 1.62505 \times 10^{-1} \]

\[ R^2 = 0.9877 \]
Followill - 18

Figure Ie

\[ y = \frac{246.28}{\exp\left(-5.03699 \times 10^{-3} \ln(x)^4 + 6.35598 \times 10^{-2} \ln(x)^3 - 7.20137 \times 10^{-2} \ln(x)^2 + 2.41153 \times 10^{-1} \ln(x) - 4.26873 \times 10^0\right)} + 1 \]

\[ R^2 = 0.9950 \]
Figure IIa

Arc Length from Center of Plaque (mm)

Dose (Gy)

Edge of Plaque
Figure IIb

Dose (Gy)

Arc Length from Center of Plaque (mm)

Edge of Plaque
Figure III

Reported COMS Doses (Gy)

COMS Doses (Gy)
Table I. Summary of generic solution fit and $R^2$ values for the combinations of plaque size and critical structures studied.

<table>
<thead>
<tr>
<th>Plaque</th>
<th>Macula</th>
<th>Disc</th>
<th>Lens</th>
<th>Apex</th>
<th>5 mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 mm</td>
<td>$3^{rd}$ order poly.*</td>
<td>$4^{th}$ order poly.</td>
<td>Linear</td>
<td>Exponential</td>
<td>Linear</td>
</tr>
<tr>
<td></td>
<td>0.9976</td>
<td>0.9939</td>
<td>0.9946</td>
<td>0.9834</td>
<td>0.9907</td>
</tr>
<tr>
<td>14 mm</td>
<td>$4^{th}$ order poly.*</td>
<td>$3^{rd}$ order poly.</td>
<td>Linear</td>
<td>Linear</td>
<td>Linear</td>
</tr>
<tr>
<td></td>
<td>0.9950</td>
<td>0.9877</td>
<td>0.9945</td>
<td>0.9656</td>
<td>0.9981</td>
</tr>
<tr>
<td>16 mm</td>
<td>$3^{rd}$ order poly.*</td>
<td>Linear</td>
<td>Quadratic</td>
<td>Quadratic</td>
<td>Linear</td>
</tr>
<tr>
<td></td>
<td>0.9997</td>
<td>0.9959</td>
<td>0.9985</td>
<td>0.9834</td>
<td>0.9987</td>
</tr>
<tr>
<td>18 mm</td>
<td>Linear</td>
<td>Linear</td>
<td>Quadratic</td>
<td>$3^{rd}$ order poly.</td>
<td>Linear</td>
</tr>
<tr>
<td></td>
<td>0.9984</td>
<td>0.9982</td>
<td>0.9911</td>
<td>0.9624</td>
<td>0.9946</td>
</tr>
<tr>
<td>20 mm</td>
<td>Quadratic</td>
<td>Quadratic</td>
<td>Linear</td>
<td>$3^{rd}$ order poly.</td>
<td>Linear</td>
</tr>
<tr>
<td></td>
<td>0.9887</td>
<td>0.9957</td>
<td>0.9975</td>
<td>0.9727</td>
<td>0.9965</td>
</tr>
</tbody>
</table>

*Solutions based on ln(X).*
Table 2 – Summary of PS/COMS dose ratios ± one standard deviation.

<table>
<thead>
<tr>
<th>Plaque</th>
<th>Macula</th>
<th>Disc</th>
<th>Lens</th>
<th>Apex</th>
<th>5 mm point</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 mm</td>
<td>0.87 ± 0.073</td>
<td>0.79 ± 0.078</td>
<td>0.93 ± 0.049</td>
<td>0.87 ± 0.029</td>
<td>0.88 ± 0.019</td>
</tr>
<tr>
<td></td>
<td>(0.72 - 1.03)</td>
<td>(0.60 - 1.03)</td>
<td>(0.78 - 1.07)</td>
<td>(0.85 - 0.95)</td>
<td>(0.85 - 0.93)</td>
</tr>
<tr>
<td>14 mm</td>
<td>0.88 ± 0.069</td>
<td>0.83 ± 0.069</td>
<td>0.92 ± 0.057</td>
<td>0.89 ± 0.028</td>
<td>0.88 ± 0.023</td>
</tr>
<tr>
<td></td>
<td>(0.64 - 1.05)</td>
<td>(0.64 - 1.03)</td>
<td>(0.68 - 1.08)</td>
<td>(0.84 - 0.94)</td>
<td>(0.84 - 0.94)</td>
</tr>
<tr>
<td>16 mm</td>
<td>0.90 ± 0.082</td>
<td>0.85 ± 0.069</td>
<td>0.91 ± 0.064</td>
<td>0.90 ± 0.033</td>
<td>0.89 ± 0.022</td>
</tr>
<tr>
<td></td>
<td>(0.62 - 1.06)</td>
<td>(0.64 - 1.07)</td>
<td>(0.60 - 1.06)</td>
<td>(0.84 - 0.98)</td>
<td>(0.83 - 0.96)</td>
</tr>
<tr>
<td>18 mm</td>
<td>0.93 ± 0.079</td>
<td>0.87 ± 0.071</td>
<td>0.92 ± 0.047</td>
<td>0.89 ± 0.020</td>
<td>0.88 ± 0.020</td>
</tr>
<tr>
<td></td>
<td>(0.73 - 1.11)</td>
<td>(0.65 - 1.09)</td>
<td>(0.79 - 1.04)</td>
<td>(0.84 - 0.93)</td>
<td>(0.82 - 0.94)</td>
</tr>
<tr>
<td>20 mm</td>
<td>0.91 ± 0.095</td>
<td>0.88 ± 0.080</td>
<td>0.92 ± 0.059</td>
<td>0.89 ± 0.020</td>
<td>0.88 ± 0.021</td>
</tr>
<tr>
<td></td>
<td>(0.62 - 1.08)</td>
<td>(0.61 - 1.07)</td>
<td>(0.68 - 1.08)</td>
<td>(0.84 - 0.95)</td>
<td>(0.83 - 0.94)</td>
</tr>
</tbody>
</table>

Values in parentheses indicate the range of doses represented by the center 95% of the data.
Appendix I

12 mm plaque

5 mm point:  \( Dose(Gy) = 0.306167943X + 1.25035437 \)

Apex:  \( Dose(Gy) = 7.7151X^{0.4218} \)

Lens:  \( Dose(Gy) = 0.6074819X - 1.849867 \)

Disc:  \( Dose(Gy) = 2 \times 10^{-7} X^4 - 1 \times 10^{-4} X^3 + 0.0194X^2 - 0.7489X + 28.479 \)

Macula:

\[
Dose(Gy) = \frac{278.3}{\exp((-0.00792246\ln(X))^3 + 0.265799(\ln(X))^2 - 0.476767(\ln(X)) - 3.64561) + 1}
\]

14 mm plaque

5 mm point:  \( Dose(Gy) = 0.2938X + 1.2257 \)

Apex:  \( Dose(Gy) = 0.0771341X + 60.8133 \)

Lens:  \( Dose(Gy) = 0.5883071X - 1.303826 \)

Disc:  \( Dose(Gy) = -5.77507 \times 10^{-6} X^3 + 0.00217836 X^2 + 0.574554 X + 0.162505 \)

Macula:

\[
Dose(Gy) = \frac{246.28}{\exp((-0.00503699\ln(X))^4 + 0.0635598(\ln(X))^3 - 0.0720137 (\ln(X))^2 + 0.241153 (\ln(X)) - 4.26873) + 1}
\]
16 mm plaque

5 mm point: \( Dose(Gy) = 0.2775X + 1.793 \)

Apex: \( Dose(Gy) = -1.91121 \times 10^{-5} X^2 + 0.0838049X + 59.5213 \)

Lens: \( Dose(Gy) = 0.0005313X^2 + 0.5357618X - 0.3455948 \)

Disc: \( Dose(Gy) = 0.8087X - 1.996 \)

Macula: \[ Dose(Gy) = \frac{213.508}{\exp(-(0.200444 \ln(X))^3 - 1.98924 \ln(X))^2 + 7.54717 \ln(X) - 12.5905)} + 1 \]

18 mm plaque

5 mm point: \( Dose(Gy) = 0.259351X + 2.80937 \)

Apex: \( Dose(Gy) = -4.23659 \times 10^{-8} X^3 + 6.87201 \times 10^{-5} X^2 + 0.0255234X + 67.3062 \)

Lens: \( Dose(Gy) = 0.001023575X^2 + 0.5222179X + 0.1143855 \)

Disc: \( Dose(Gy) = 0.861483X - 2.93996 \)

Macula: \( Dose(Gy) = 0.935159X - 2.14027 \)
20 mm plaque

5 mm point: \( Dose(Gy) = 0.2468532X + 2.524272 \)

Apex: \( Dose(Gy) = -9.10479 \times 10^{-6}X^3 + 1.67322 \times 10^{-4}X^2 - 0.0391238X + 76.9125 \)

Lens: \( Dose(Gy) = 0.642258X - 2.389035 \)

Disc: \( Dose(Gy) = 0.0014789X^2 + 0.705167X + 1.97634 \)

Macula: \( Dose(Gy) = -0.000657704268X^2 + 1.04723002X - 5.76118887 \)