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

Amanda Krintz, David S. Followill, Michelle Melia
and William F. Hanson

Department of Radiation Physics
The University of Texas M.D. Anderson Cancer Center,
Houston, TX 77030

Introduction

Choroidal melanoma is the most prominent malignant ocular tumor in adults. Standard treatment since the early 1900's has been enucleation of the involved eye. However, beginning in the 1930's radiation therapy was proposed as a treatment that would allow the patient to keep their eye, and possibly some vision. While multiple isotopes have been tried throughout the years, the current choice for eye plaque therapy is I-125. I-125 is a low energy emitter and therefore is less of a radiation hazard to personnel and other structures in the patient's body. While radiation plaque therapy has been used for many years, there has never been a decision reached as to which therapy, enucleation of the eye or eye plaque radiotherapy, provides the better control and survival. In 1986 the Collaborative Ocular Melanoma Study (COMS) began a multicenter clinical trial to compare the role of radiotherapy vs. enucleation. The trial was a randomized study with the two arms being enucleation and radiotherapy. This study in particular was designed to study medium sized tumors, defined as unilateral tumors that range from 2.5mm in height to 10.0mm. The tumor could also be no more than 16mm in diameter.

This trial accrued 1317 patients between 1987 and 1998 of which 657 were enrolled in the radiotherapy arm. The radiotherapy arm was then treated with a COMS eye plaque, which was available in 5 sizes: 12, 14, 16, 18, and 20 mm diameter. (See Figure 1) The plaque was chosen to cover the tumor with a 2-3mm margin around the outside, unless the tumor was too close to the optic nerve, in which case exceptions could be made. The initial prescription dose to the apex of the tumor, or to 5mm from the interior surface of the sclera, was 100Gy which was changed to 85Gy in 1996 when the TG-43 dosimetry formalism was applied.

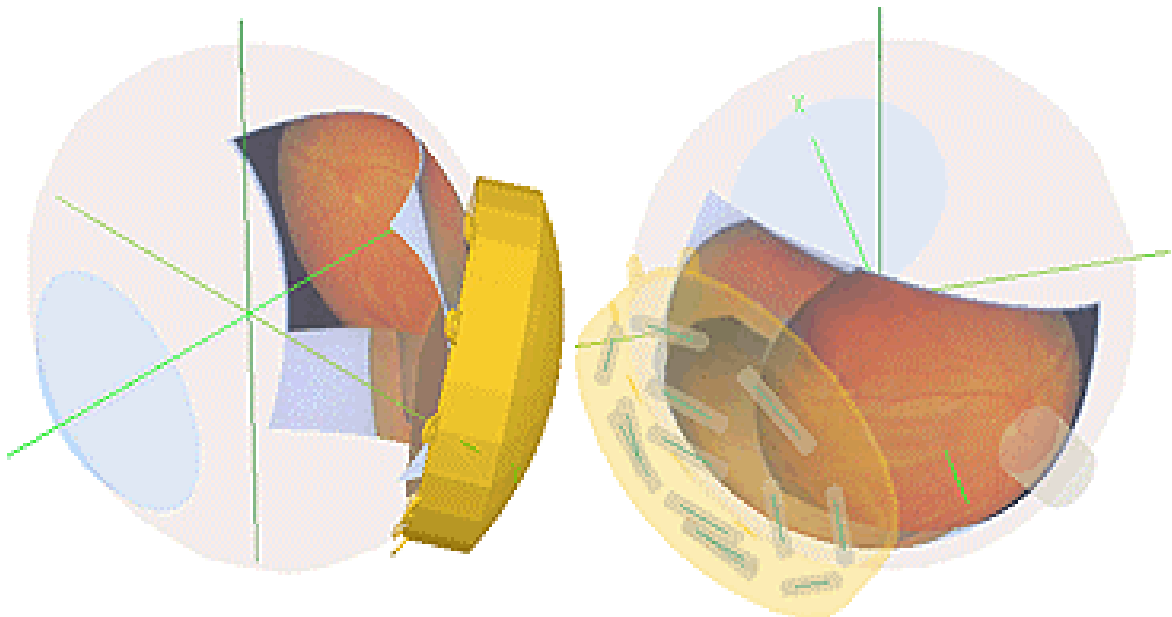


Figure1 - Example COMS Plaque

Following the completion of the trial, patient follow-ups were continued and at present, the majority of the patients have been followed for 5 years. Using the follow-up data, an analysis was then undertaken by the COMS Coordinating Center to determine any differences in survival between the two arms, as well as to find any correlation between the dose given to critical structures (macula and optic disc) in the eye and the visual acuity outcomes of the patients in the radiotherapy arm. There was no statistical difference in survival between the two arms, as well as very little correlation between the dose to the critical structures and the visual acuity outcome in the radiotherapy arm. (Collaborative Ocular Melanoma Study Group, *Ophthalmology* 108:2, February 2001)

The fact that there was very little correlation between dose and visual acuity outcome has caused the dosimetry calculations used in the trial to come under discussion. The trial was started in 1986 and as a result the dosimetry calculations used in the COMS trial are less accurate than current formalism. For this reason, the Radiological Physics Center has undertaken the project of recalculating the radiation dosimetry calculations using updated information and calculational procedures.

Overall Study

The original COMS dosimetry calculations made several assumptions. They assumed that the I-125 seed was a point source (no anisotropy), no side attenuation from the gold backing or silastic insert, and no backscatter from the gold. These assumptions cause significant differences in the dose calculations.

Taking into account the gold backing, anisotropy, and silastic insert one can provide a more accurate dose calculation which could be used to determine a more clinically relevant outcome analysis. This is the project which is currently underway at the Radiological Physics Center at M.D. Anderson Cancer Center. Once the recalculation process has been completed, a new correlation analysis will be done in cooperation with the COMS coordinating center.

Specific Objectives

(1) Use the Radiological Physics Center's (RPC) COMS calculation formalism to assess the commercial software systems ability to calculate doses based on the COMS assumptions to establish a baseline agreement.

(2) Use radiochromic film to determine the validity of a commercial software system that encompasses gold backing, anisotropy, and the silastic insert into the calculations.

(3) Using the validated commercial software, recalculate a sampling of the patients using the updated dosimetry parameters.

(4) Generate a generic solution, based on the recalculated sample, for each plaque size and individual critical structure to perform the recalculation for the entire patient database.

(5) Correlate the new dose calculations with visual acuity outcome.

Materials and Methods

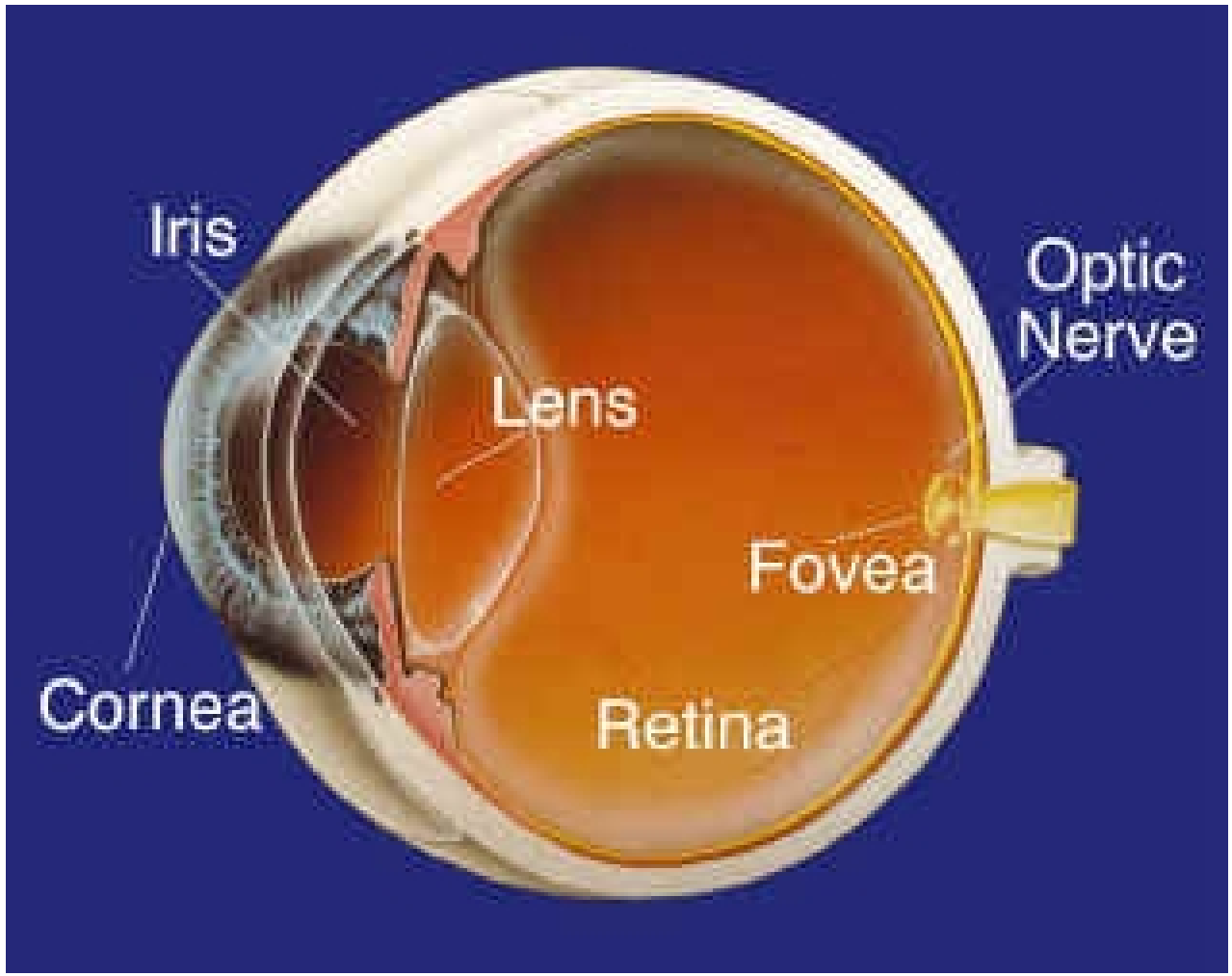


Figure 2 - Eye diagram (Fovea = Macula)

- **Determine tumor location relative to macula and other critical structures for all patients**
  - Requires use of COMS database and COMS clinically reported chord lengths
  - COMS chords: MT = macula to tumor margin

    BM = base dimension of tumor at center in the direction from the macula

    DT = disc to tumor margin

    BD = base dimension of tumor at center in the direction from disc
  - Calculate chord length from center of tumor base to macula.

    Macula to tumor center = 22mm sin(theta(m)/2)

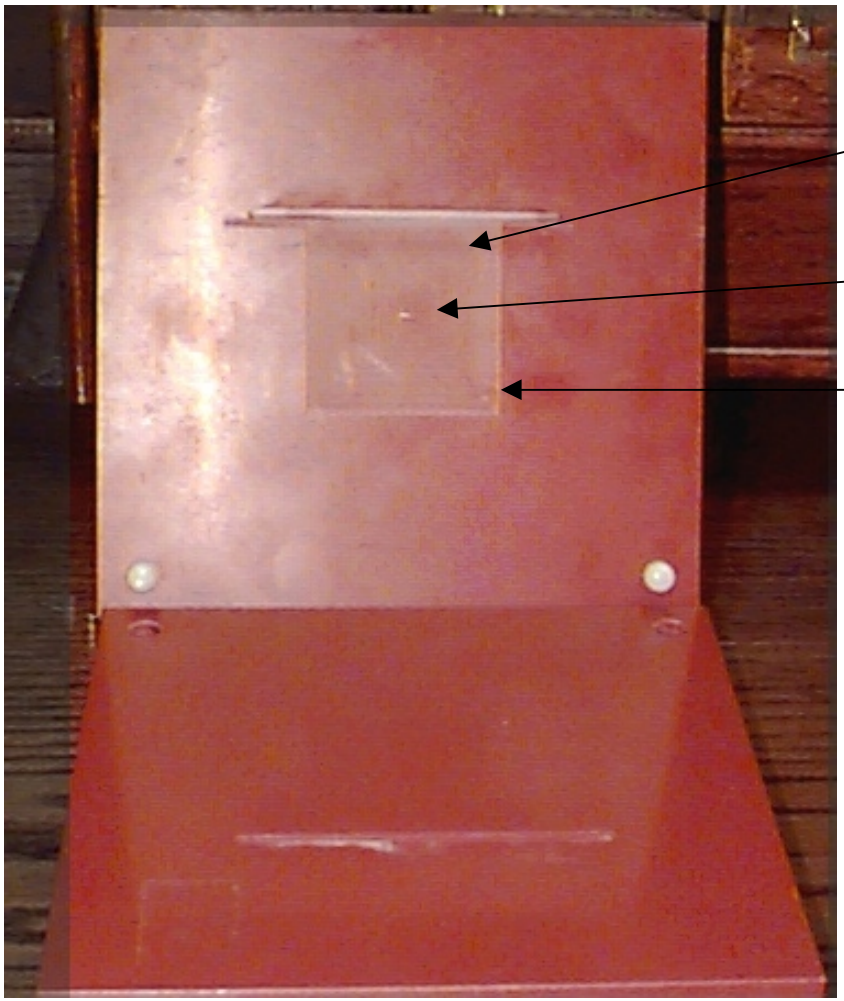
    where theta(m) = 2 $\sin^{-1}$(MT/22mm)+$\sin^{-1}$(BM/22mm)
  - Determine arc length from center of tumor base to critical structure.

$$L_a^b = \int_a^b \sqrt{1+\left[f'(x)\right]^2}\,dx$$

    Where f(x) is the equation for a sphere with radius 11mm.

- **Use Plaque Simulator(PS), ©BEBIG, to perform recalculations**
  - Establish baseline agreement between PS and the RPC calculational formalism for the original COMS assumptions.
    - This required making corrections to PS in regards to the seed coordinates used to model the COMS eye plaque geometry.
    - Run PS with the updated dosimetry parameters for a randomly chosen group of patients for each plaque size.
- **Verify Plaque Simulator with I-125 (model 6711) dosimetry measurements.**
  - Radiochromic film and solid water block phantom
    - assess dose response
    - assess film uniformity
    - assess film fading
    - assess film edge effects
  - Solid water eye phantom (future work)
    - assess dose distribution around eye plaque
    - compare measured dose distribution to that generated by PS.

Film Phantoms

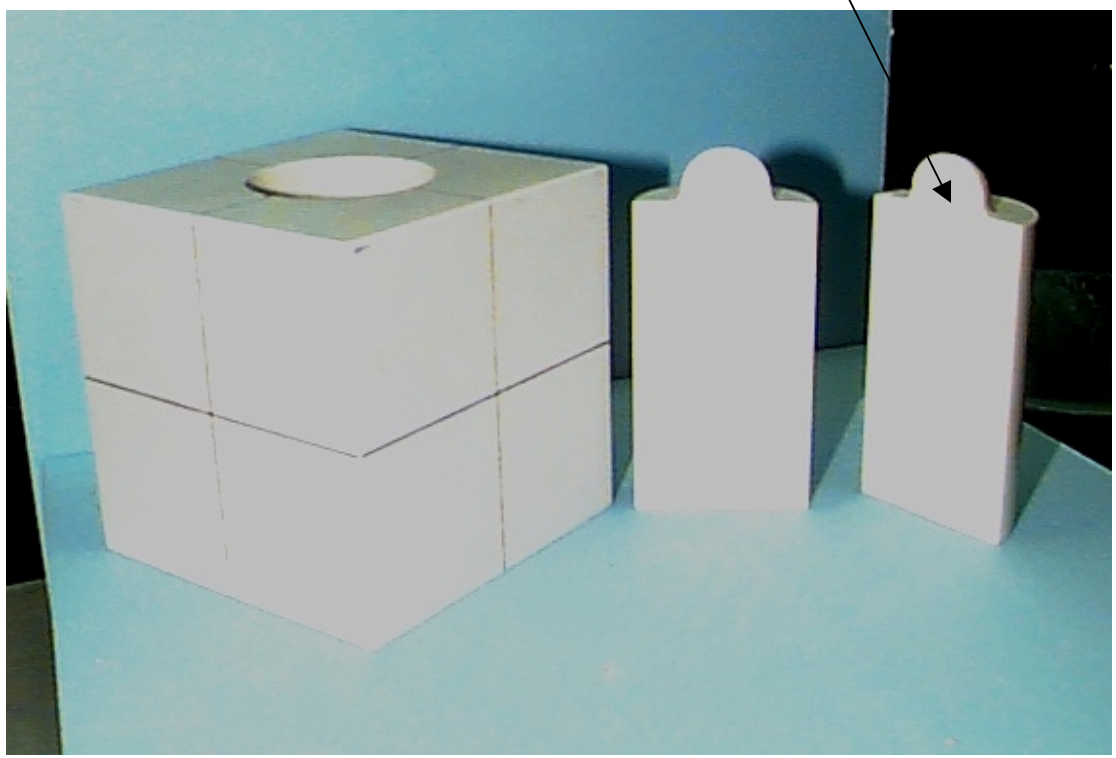


Film Cutout (6.5cm x 6.5 cm)

Seed Cutout (0.8mm x 4.5mm)

Pin to Mark Film

Film Cutout

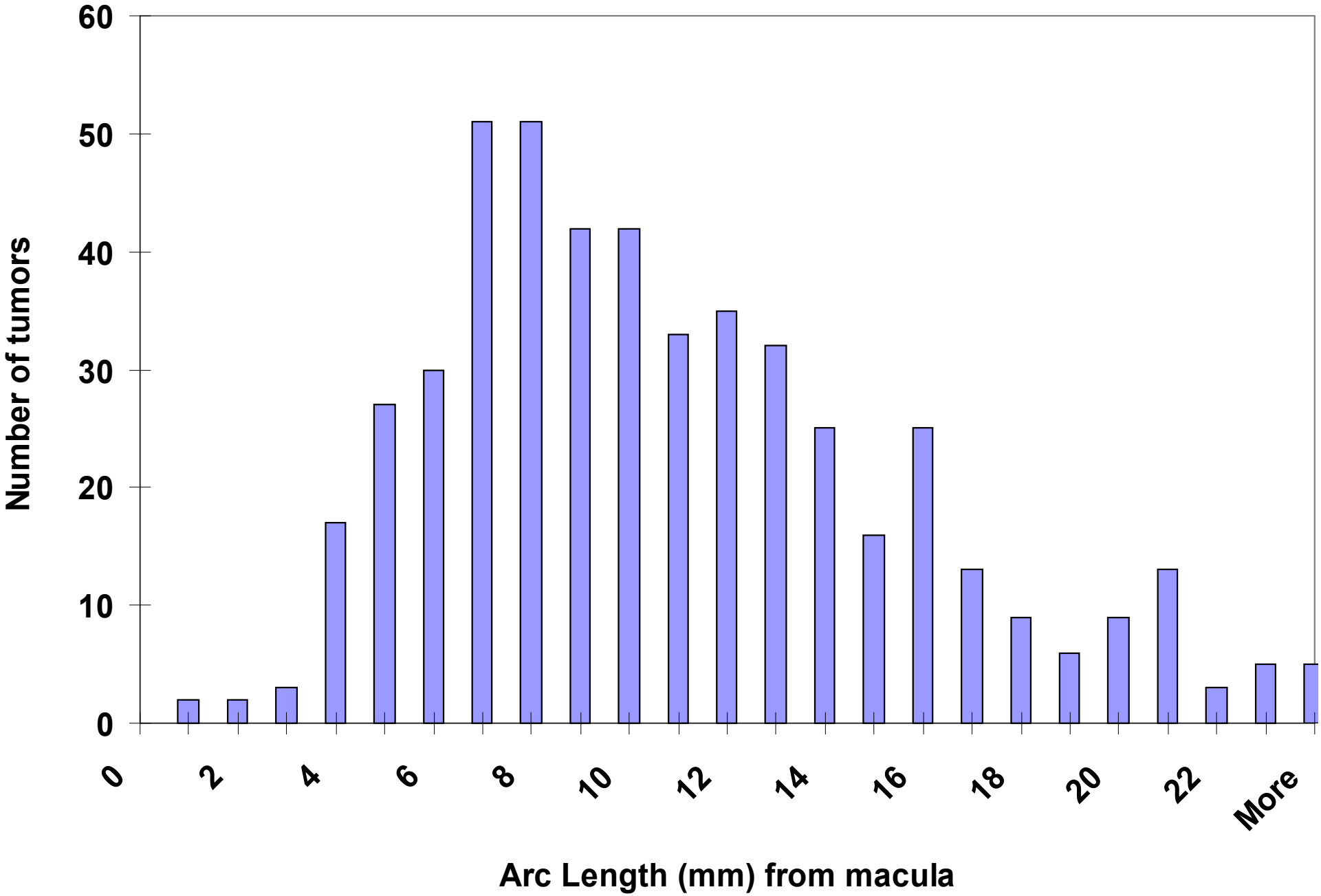


- **Determine a generic solution to perform recalculations of all patients**
  - Use a small subset of patients recalculated with PS for each plaque size
    - This should include the maximum and minimum arc lengths for the given structure
  - Generate a generic mathematical solution using plaque and loading characteristics available in the COMS database
    - solution generated using **X** vs. dose

    X = #seeds * Activity per seed (U) * Duration (hr) / arc length^2
  - Test the generic solution against a second set of patients recalculated by hand.

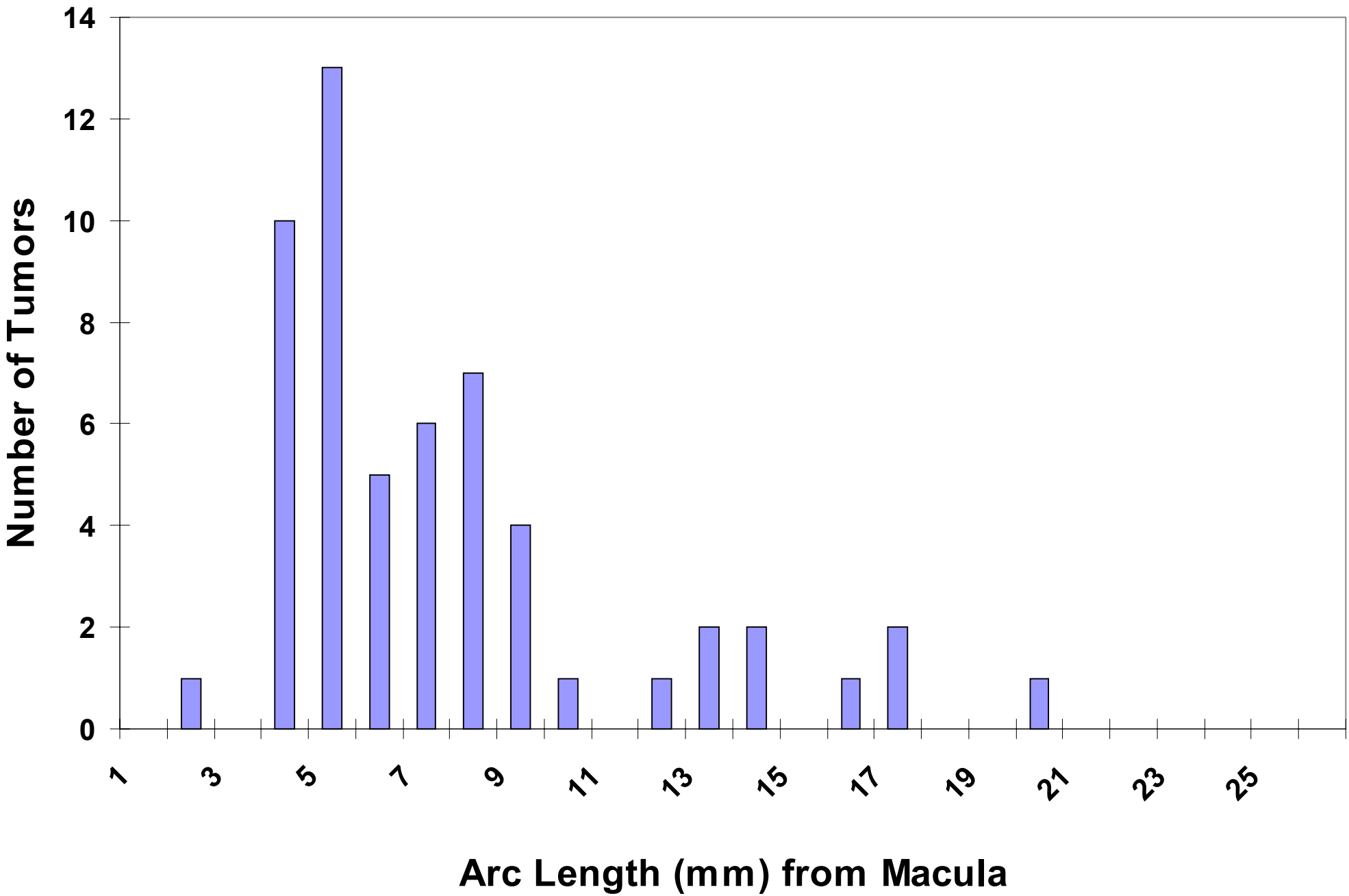
The majority of the tumors were in the posterior hemisphere of the eye, in close proximity to the macula and optic disc. This determination reinforced the need for recalculated doses, as the dose gradient is very high in the area surrounding the plaque, and the differences due to the updated parameters can be significant.

Tumor locations

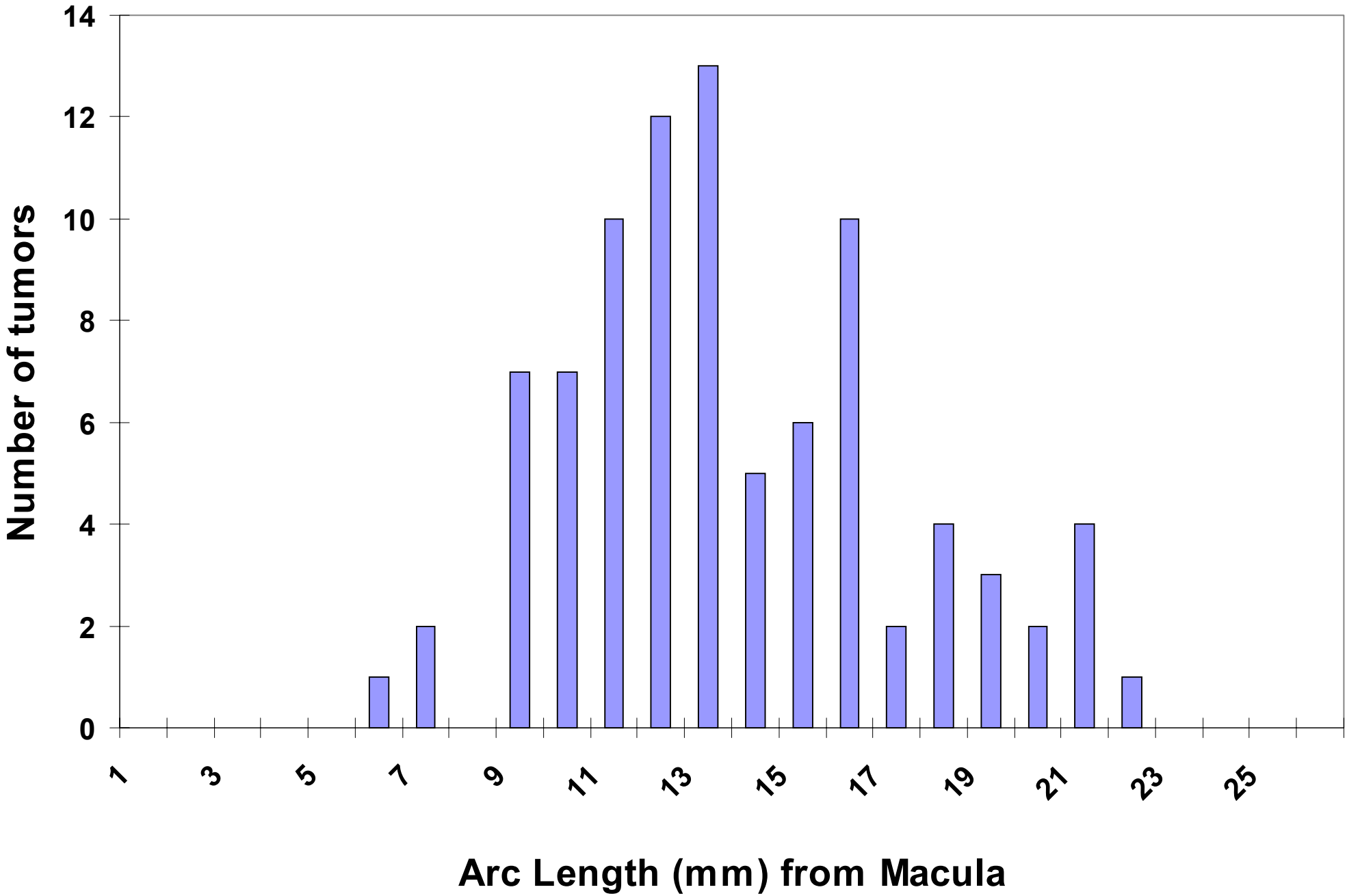


When looking at the tumor locations by plaque size, it was found that the smaller tumors were even more posterior than the largest tumors.

Tumor Locations for 12mm Plaque

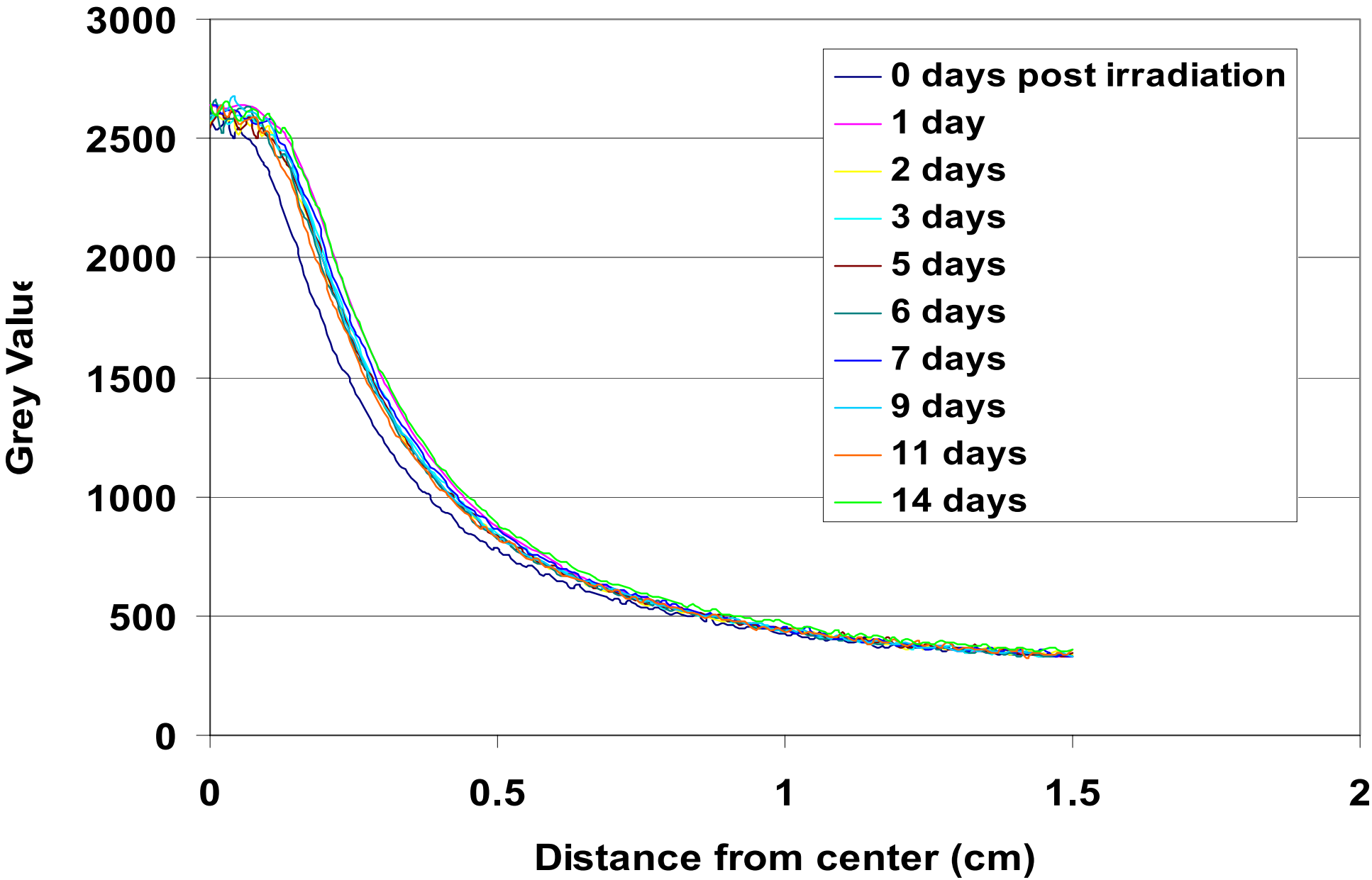


Tumor Locations for 20mm Plaque



* Measurements

The original irradiations to 500Gy showed that the film had reached saturation. Six irradiation's to 500Gy were obtained and used to characterized the fading characteristics of the film. The fading characteristics were found to be unchanged for the I-125 energy, as compared to the higher energy characteristics which are well known. It was found that the film continued to darken for the first 48-72 hours, but was then relatively stable over the next two weeks.


3000
2500
2000
1500
1000
500
0
Grey Valu
0
0.5
1
1.5
2
Distance from center (cm)
0 days post irradiation
1 day
2 days
3 days
5 days
6 days
7 days
9 days
11 days
14 days

* Comparison of Software

The software comparison between the RPC and Plaque Simulator COMS calculation initially showed an error in the Plaque Simulator geometry of the COMS plaques. The 16mm and 20mm seed locations did not agree with those used in the original COMS calculations. This was remedied and agreement between the PS base calculation and the original RPC COMS calculation was found to be within 5% for nearly every critical structure and plaque size for a representative test case. This was deemed acceptable and the project then continued.

PS COMS calculation / Original RPC COMS calculation Ratio

Plaque Size	Inner Sclera	Macula	Optic Disc	Tumor Apex	5mm (CAX)	Lens
12mm	0.965	0.989	0.968	0.982	0.992	0.996
14mm	1.017	0.976	0.978	0.995	0.994	0.998
16mm	1.002	0.990	0.956	0.990	0.992	0.992
18mm	1.041	0.955	0.929	1.009	1.000	0.992
20mm	0.999	1.024	0.944	0.988	0.989	0.988

Following the validation and correction of the base COMS calculation, the Plaque Simulator software was then used to recalculate a random sampling of patients with updated parameters to compare with the original COMS calculation. This result gave an indication of the change expected, and also gave an initial validation of the software calculations as they agreed within published data as to how the parameters should effect the final dose calculation.

Updated PS Calculation / RPC COMS Ratio

Plaque Size	Inner Sclera	Macula	Optic Disc	Tumor Apex	5mm (CAX)	Lens
12mm	0.845	0.899	0.893	0.885	0.889	0.908
14mm	0.847	0.883	0.860	0.886	0.890	0.911
16mm	0.857	0.898	0.896	0.889	0.890	0.916
18mm	0.858	0.890	0.894	0.889	0.891	0.914
20mm	0.858	0.900	0.903	0.893	0.891	0.921

* Generic Solution

The results of the generic solution were very good. The generic solutions were determined for the macula, optic disc, lens, tumor apex, and the 5mm central axis point for each plaque size. The table below shows how many patients were used in the initial random sampling that was recalculated to generate the generic solution. There were then 4 random patients recalculated for each plaque size to "check" the generic solution. These results are shown in Figure 7. Examples of the generic solution determination and check patients are displayed in panels A-C for various plaque sizes and critical structures.

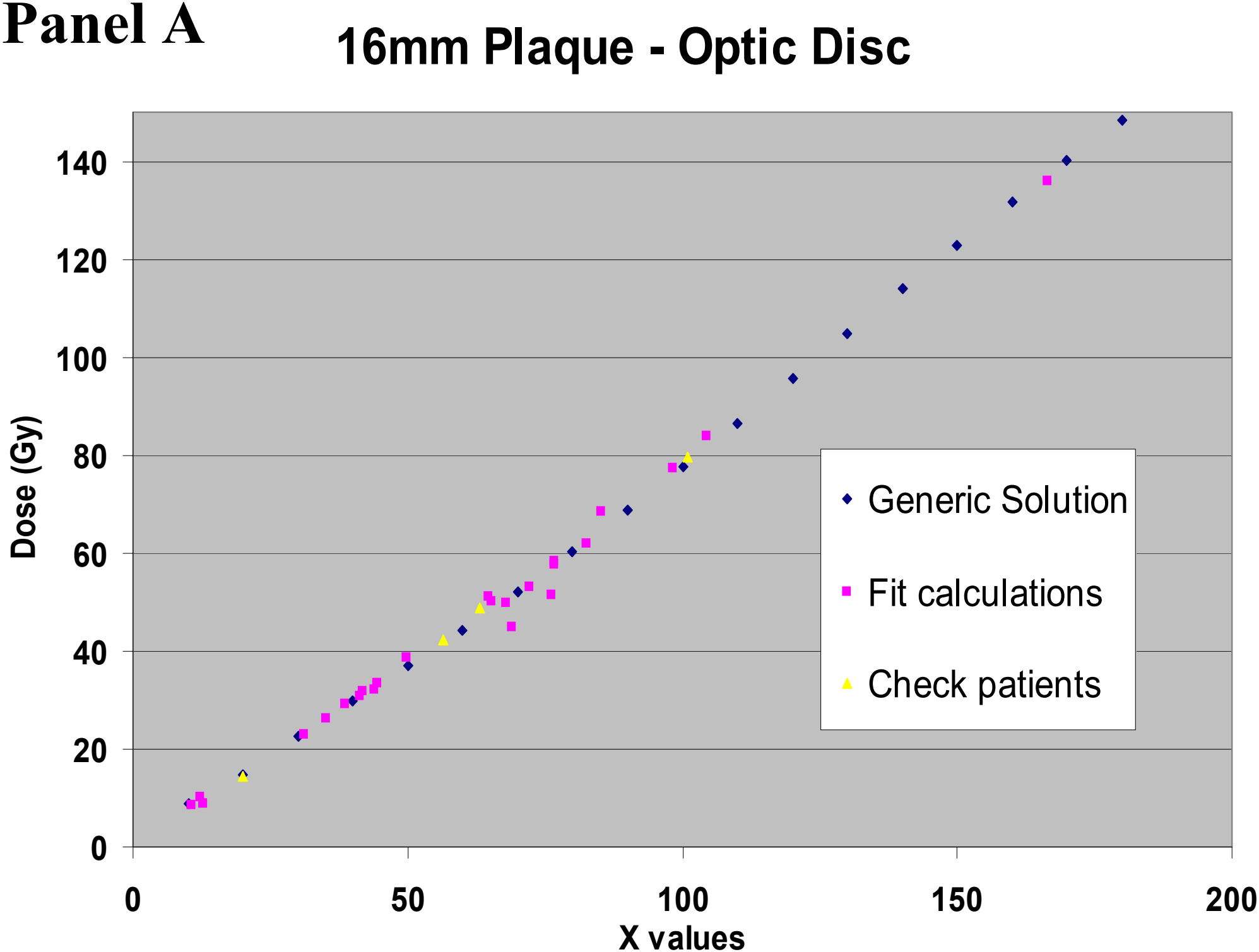
Plaque Size	Total # of Patients	# in random sample
12mm	56	16
14mm	96	16
16mm	128	26
18mm	96	18
20mm	89	15

Generic Solution / “Check Patient” Recalculation Ratio

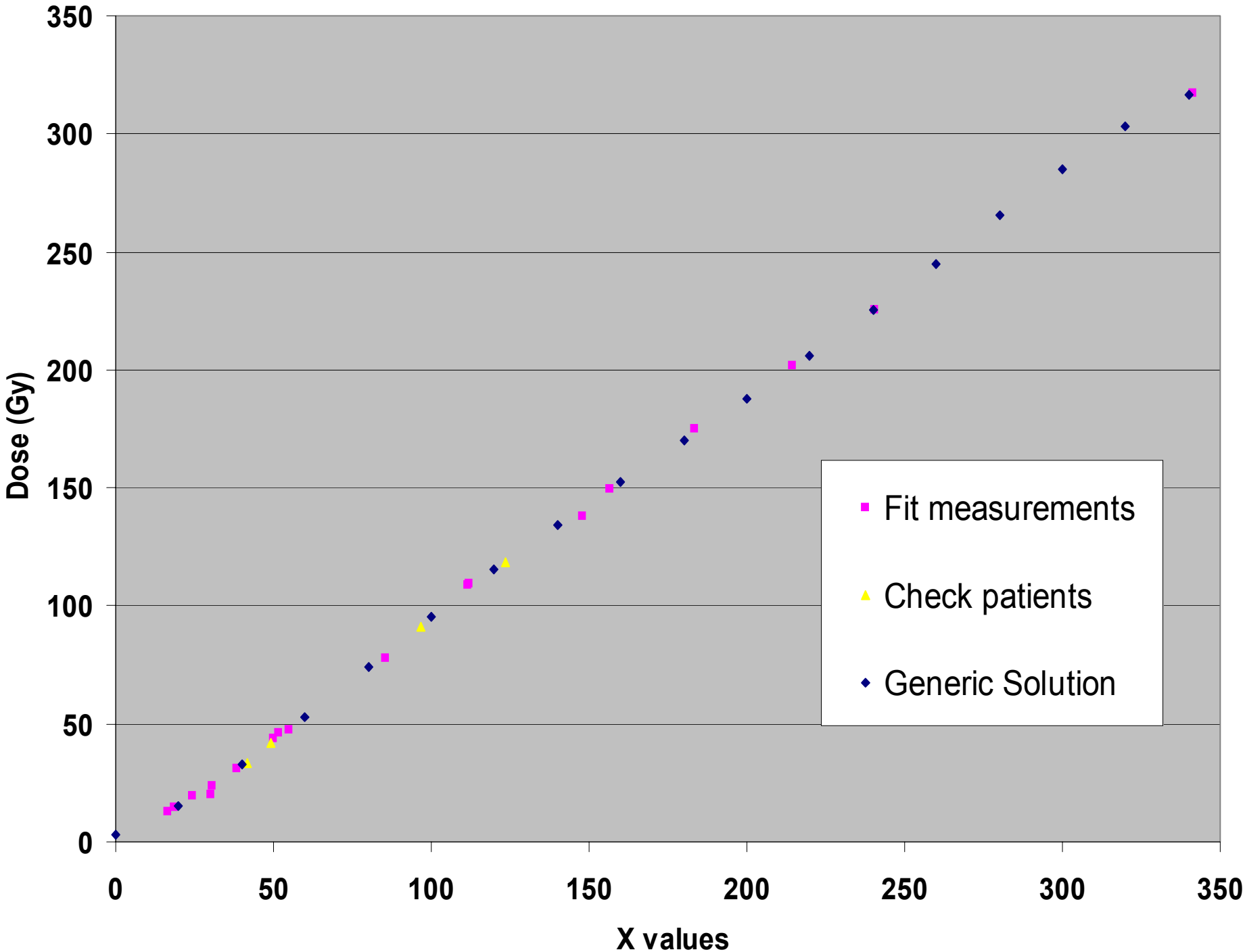
Plaque Size		Macula	Disc	Lens	Apex	5mm
12mm		1.008	1.004	0.986	0.994	0.997
14mm		1.012	0.996	0.989	0.979	1.007
16mm		0.995	0.986	0.963	0.984	0.990
18mm		1.006	0.992	0.981	1.001	1.006
20mm		0.972	1.027	0.965	1.017	1.016

Figure 7- Accuracy of Generic Solution

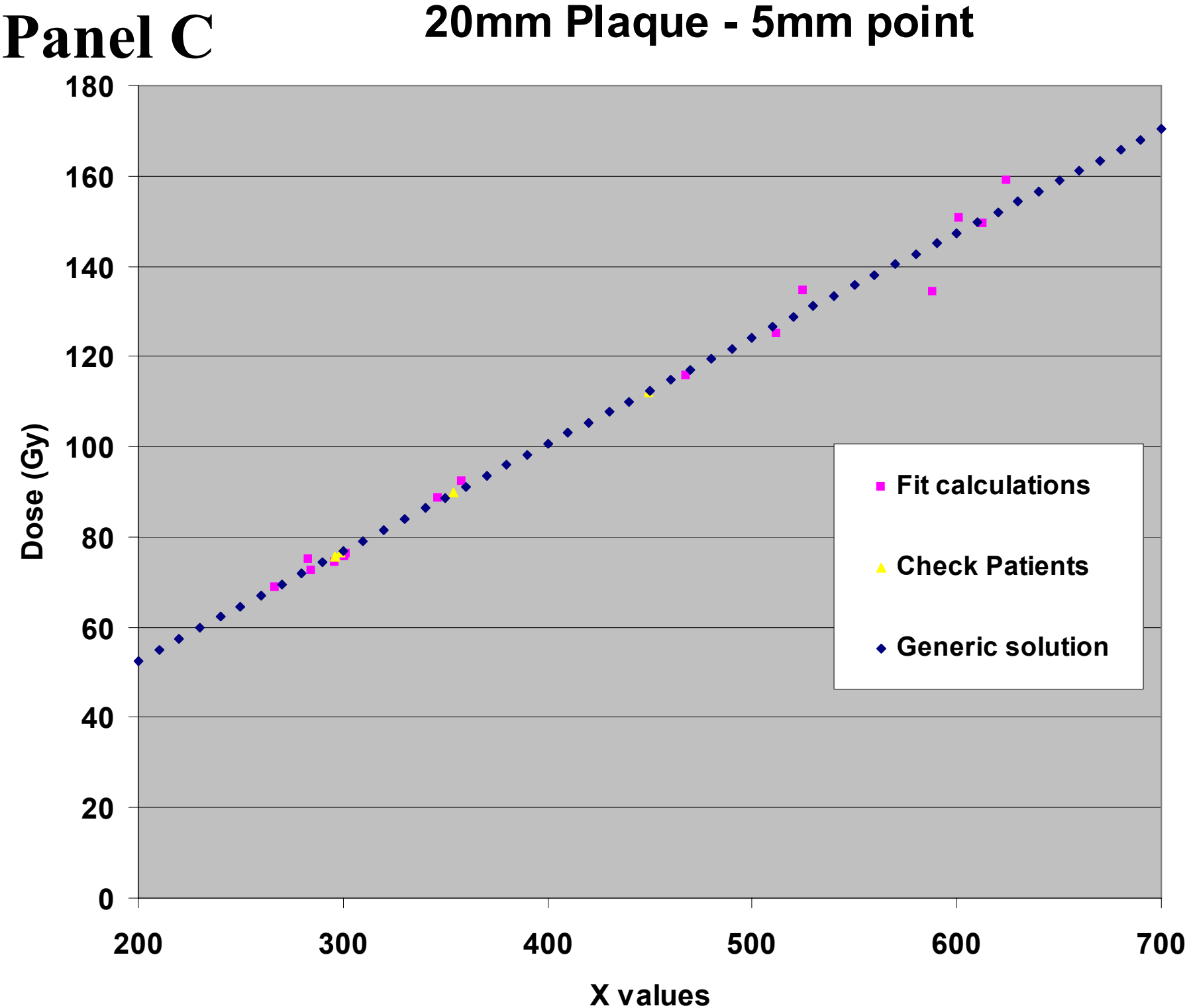
Panel A


16mm Plaque - Optic Disc
Dose (Gy)
0
20
40
60
80
100
120
140
0
50
100
150
200
X values
Generic Solution
Fit calculations
Check patients

Panel B


18mm plaque - Macula
Dose (Gy)
X values
0
50
100
150
200
250
300
350
Fit measurements
Check patients
Generic Solution

Panel C


20mm Plaque - 5mm point
Dose (Gy)
180
160
140
120
100
80
60
40
20
0
200
300
400
500
600
700
X values
Fit calculations
Check Patients
Generic solution

Conclusions

- The majority of the tumors were located in the posterior hemisphere of the eye in close proximity to the macula and optic disk.

- A generic solution can be determined from a random sampling of the patient database that is accurate enough to then calculate the rest of the recalculated doses.

- The commercial software, Plaque Simulator, can calculate doses that agree with RPC calculations using the COMS assumptions.

- FUTURE WORK - Perform new correlation analysis of recalculated doses to critical structures vs. visual acuity outcome.

This investigation was supported by PHS grant EY 06266, The Physics Center for COMS, awarded by the NEI, DHHS.

For a copy of this poster go to
http://rpc.mdanderson.org