

# Iodine-125 Brachytherapy for Uveal Melanoma: A Systematic Review of Radiation Dose

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## Keywords

Uveal melanoma · Brachytherapy · Radiation dose · COMS trial

## Abstract

**Aim:** To investigate whether lower radiation doses may yield similar outcome measures to those from the COMS trial.

**Methods:** A literature review of English language articles was performed using the PubMed database of the U.S. National Library of Medicine and the Cochrane Central Register of Controlled Trials using the following keywords: uveal melanoma, choroidal melanoma, primary uveal malignant melanoma, iodine-125 brachytherapy, local recurrence, local treatment failure, and local tumor control. The relationships between study local recurrence rate and median dosage were tested by linear regression, with each study weighted by the number of patients included. **Results:** Fifteen retrospective and prospective studies were selected for systematic review (2,662 patients). Ranges of reported mean or median radiation dose to tumor apex were 62.5–104.0 Gy. Local recurrence rates ranged from 0 to 24%. A 1.0-Gy increase in the average study dose was associated with a 0.14% decrease in local recurrence rate, which was not statistically sig-

nificant ( $p$  value 0.336). **Conclusion:** The gold standard empirically derived 85.0-Gy radiation dose for the treatment of uveal melanoma could be tested in a randomized study.

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## Introduction

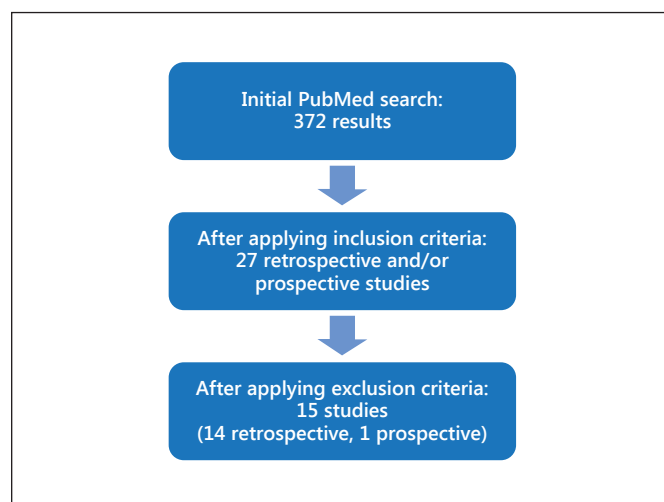
### *Historical Background*

The treatment of uveal melanoma has evolved significantly, from enucleation to eye-preserving episcleral plaque brachytherapy, since the first implantation of mesothorium (radium-228) capsules in fractionated doses by Deutschmann [1] in Germany in 1915 [2]. R. Foster Moore [3] introduced intralesional implantation of radon seeds in England in 1929. A 1-millicurie seed was implanted for 2 weeks, but the tumor was later retreated with implantation of a 5-millicurie seed, due to the lack of tumor regression observed 3 months following initial treatment. One year following the first implantation, it was shown that the tumor had regressed and vision was preserved. In 1966, Lommatzsch and Vollmar [4] were among the first to describe dose parameters in the treat-

ment of uveal melanoma with the use of ruthenium-106 applicators [2]. In their case series, they reported contact scleral doses between 20,000–60,000 rads (200.0–600.0 Gy). Although they did not state an apical dose, with a maximal contact scleral dose of 600.0 Gy, approximately 10% of isodose is expected at the depth of 6.8 mm. Therefore, a tumor measuring 7.0 mm would have been only treated with 60.0 Gy to tumor apex (10% of contact scleral dose of 600.0 Gy), which could explain their relatively large amount of local recurrences or re-treatments needed (approximately 30%).

In the 1960s, H.B. Stallard [5, 6] popularized the use of cobalt-60 episcleral plaques to treat choroidal melanomas. His initial clinical data and calculations from isodose curves suggested that episcleral brachytherapy delivering a range of 7,000–14,000 rads (equivalent to 70.0–140.0 Gy) to the tumor apex could be a globe-preserving therapeutic alternative to enucleation with non-inferior mortality rates. Due to the commercial availability of standardized cobalt plaques, the fact that the long half-life allowed for reuse, and the reproducibility of the technique, Stallard established this protocol as the best alternative to enucleation [7]. In the 1970s, Rotman et al. [8] reported survival rates similar to enucleation using cobalt-60 applicators with a dose of 85–100 Gy. They expressed their single-institution opinion based upon an unspecified number of patients that higher dose rates (50 rads/h) provided more effective local control than the lower dose rates (30 rads/h) with the same total dose of 8,500 rads to the tumor apex. Interestingly, they suggested that lowering total doses may be possible if an adequate dose rate was maintained. No statistical proof of these statements was reported.

Subsequent efforts to reduce the incidence of radiation-induced complications led to the introduction of low-emitting isotopes such as iodine-125. In the 1970s, the transition to iodine-125 plaques was led by Rotman and Packer [7–10], when dosimetric comparisons between cobalt-60 and iodine-125 isotopes showed that for a depth of 10 mm there is basically no difference in dose penetration, and for depths at 15 mm there is only a 5% reduction in dose penetration of iodine-125 when compared to cobalt-60 [9]. The Greene melanoma rabbit model provided histological evidence of iodine-125 sparing adjacent tissue such as the lens and retina at more favorable rates than cobalt-60 brachytherapy [9]. The latter findings, in addition to a much safer profile by iodine-125 for both the patient and surgeon, given the ability to shield its radioactivity with merely a 0.5-mm gold sheet cover, led to the establishment of iodine-125 plaques as most widely used isotope for brachytherapy [11].



**Fig. 1.** Flow diagram of systematic review of literature and study selection.

### Current Practices

Beginning in 1986, the Collaborative Ocular Melanoma Study (COMS) was the first prospective randomized clinical trial comparing iodine-125 plaque brachytherapy with enucleation for patients with medium-sized tumors. The minimal radiation dose to the tumor apex used in the COMS trial was 85.0 Gy. A minimum of 85.0 Gy was prescribed to the depth of 5.0 mm from the inner sclera for tumors less than 5.0 mm in apical height. This dose was adjusted (originally 100.0 Gy) after the Task Group (TG 43) protocol was adopted by the American Association of Physicists in Medicine [12]. The dose of 85.0 Gy for the COMS trial was selected based upon expert consensus [9, 11, 13–15]. The COMS study showed that an eye-preserving, and potentially a vision-preserving, therapeutic regimen with iodine-125 plaque brachytherapy had a non-inferior mortality risk compared to enucleation up to 12 years following treatment [16]. These data established iodine-125 brachytherapy as the gold standard for treating medium-sized uveal melanoma with the 5-year risk of local treatment failure of 10.3% [17]. Published studies have suggested that local recurrence increases the potential for metastasis [18–21].

### Study Question

The lack of evidence regarding optimal plaque radiation dose presents an opportunity to investigate whether doses lower than the COMS standard of 85.0 Gy to the tumor apex would provide a comparable therapeutic profile with a non-inferior local control rate [17]. To our

**Table 1.** Characteristics of selected retrospective and prospective

Study (first author)	Year	Type of study	Isotope	Mean dose, Gy	Patients, <i>n</i>	Local recurrence rate, %	Mean largest basal diameter, mm	Mean tumor height, mm	Mean follow-up, months
<i>With echographic confirmation</i>									
Tabandeh [22]	2000	retrospective	iodine-125	85	117	1.7	9.6	4.2	37
Saconn [23]	2010	retrospective	iodine-125	62.5	62	8.7	11.4	4.6	58 (median)
McCannel [24]	2012	retrospective	iodine-125	85	170	0	10.8	4.8	32.4
Badiyan [25]	2014	retrospective	iodine-125/ supplemental TTT	97.8	526	3.6	12.2	4.2	53.4
Murray [26]	2013	retrospective	iodine-125	85	55	1	10.7	3.3	145.2
Aziz [27]	2016	retrospective	iodine-125 and ruthenium-106	85	198	1.5	11.3	4.1	25.6
<i>Without echographic confirmation</i>									
Jampol (COMS) [17]	2002	prospective randomized	iodine-125	85	650	10.3	11.5	4.2	60
Puusaari [28]	2003	retrospective	iodine-125	87 (median)	97	6	16.1	10.7	43
Jensen [29]	2005	retrospective	iodine-125	104 (median)	156	7	11.2	4	74 (median)
Correa [30]	2009	retrospective	iodine-125	82.9	120	11.6	12.2 (median)	5.9 (median)	50.4 (median)
Leonard [31]	2011	retrospective	iodine-125	85	37	24	12.3	6.3	100
Karlovits [32]	2011	retrospective	iodine-125	86	35	0	13.5	7.8	60
Berry [14]	2013	retrospective	iodine-125	85	82	2.4	10.7	4.6	46.8 (median)
Perez [15]	2014	retrospective	iodine-125		190	9	11.0 (median)	3.9 (median)	49.2 (median)
				<69	48	6			
				69–81	47	11			
				81–89	48	15			
				>89	47	4			
Wisely [34]	2016	retrospective	iodine-125	85.8 (median)	113	5.3	10.5 (median)	4 (median)	65.5 (median)
Aziz [27]	2016	retrospective	iodine-125 and ruthenium-106	85	54	9.3	11.1	3.6	50.4

knowledge, there has been no systematic review of retrospective or prospective clinical studies evaluating the relationship between dose to tumor apex and local recurrence rates of patients with uveal melanoma treated with iodine-125 brachytherapy. This study aims to investigate whether lower radiation doses may yield similar outcome measures to those from the COMS trial, specifically as related to local control during the initial 5 years of post-treatment brachytherapy. Having lower radiation doses with a comparable local recurrence rate would represent a more efficient treatment profile that would limit secondary side effects from dose-related radiation toxicity.

## Materials and Methods

Since our study involves a review of previously published peer-reviewed literature, no institutional approval was required. Our literature review of English language articles was performed using the PubMed database of the U.S. National Library of Medicine and the Cochrane Central Register of Controlled Trials of the Cochrane Library using the following keywords: uveal melanoma, choroidal melanoma, primary uveal malignant melanoma, io-

dine-125 brachytherapy, local recurrence, local treatment failure, and local tumor control. Our initial search yielded 327 reports. We then applied the following inclusion criteria: (1) English language articles, (2) primary intervention with iodine-125 brachytherapy, (3) reported mean or median radiation dose to tumor apex, (4) reported local recurrence rate (%), (5) reported mean tumor dimensions of largest basal diameter and apical tumor height, and (6) reported mean follow-up time of 30 months (Fig. 1). These yielded a total of 27 studies. We then excluded those studies in which the dose to tumor apex had not been adjusted to the TG-43 protocol recommendations, which led to a final selection of 15 studies (14 retrospective, 1 prospective). The characteristics of each study selected for review included: number of patients, mean radiation dose to tumor apex (Gy), local recurrence rate (%), mean tumor largest basal diameter (mm), mean tumor apical height (mm), and mean follow-up time (months). For those studies that reported multiple data points corresponding to different lengths of follow-up, the local recurrence rate closest to 5 years (60 months) posttreatment follow-up was selected for our review (Table 1).

The relationships between study local recurrence rate and study features, like median dosage or median follow-up time, were tested by linear regression, with each study weighted by the number of patients included. All statistical analysis was conducted in R version 3.2.3. A regression coefficient was considered significant if the *p* value was <0.05.



patients having a tumor height between 2.5 and 5.0 mm. In 2013, Murray et al. [26] reported no significant differences in local control rates between patients treated with an adjusted dose to the apical height and those treated with the standard COMS design dose of 85.0 Gy to a depth of 5.0 mm. The latter study suggested that dose to the true apical height may render a lower incidence of radiation-related complications. In another retrospective case study of 190 patients, Perez et al. [15] showed data stratified by varied dose quartiles (<65.0 to >85.0 Gy) and reported no association between dose to tumor apex and rate of local failure (9%), which was similar to the COMS trial despite having significantly reduced doses in 50% of their patients. By stratifying their treatment groups to different dose quartiles, they also found a direct relationship between radiation dose and ocular toxicity. They suggested a dose to the tumor apex of less than 85.0 Gy especially for tumors less than 5.0 mm in height. Although the above-mentioned studies argue in favor of a dose reduction for episcleral brachytherapy in the treatment of uveal melanoma, their retrospective designs and few numbers of patients limit their statistical power.

Our review of 2,662 patients from 15 clinical studies is the largest analysis of its kind comparing doses to tumor apex in relation to local control rates. Our study entails a systematic review of retrospective studies showing local control rates of uveal melanoma after treatment with episcleral iodine-125 brachytherapy. One of the limitations

of our study is the inclusion of retrospective studies due to lack of prospective, randomized trials, which makes it difficult to perform a formal meta-analysis. This is due mainly to the lack of existing prospective, randomized trials for the treatment of uveal melanoma with episcleral iodine brachytherapy beyond the COMS trial. Any future prospective studies will have to standardize methodology of tumor height measurements and adjust for dosimetric variations due to episcleral plaque designs.

The systematic review of published data suggests that the gold standard for the treatment of uveal melanoma with iodine brachytherapy using a radiation dose of the empirically derived 85.0 Gy to tumor apex could be tested in a randomized study. Tumors less than 5.0 mm in height from lower doses adjusted to true apical height rather than those established by the COMS trial need further assessment.

### Statement of Ethics

The study complied with the guidelines for human studies and animal welfare regulations. The subject gave informed consent and the study protocol was approved by the institute's committee on human research.

### Disclosure Statement

The authors have no conflicts of interest to declare.

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