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# Ruthenium-106 plaque brachytherapy for uveal melanoma: Factors associated with local tumor recurrence

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#### **Abstract**

**PURPOSE**—Plaque brachytherapy is a common form of treatment for uveal melanoma, and the Collaborative Ocular Melanoma Study (COMS) employed I-125. Recently, Ru-106 has been reintroduced for plaque brachytherapy in the United States. We reviewed our experience treating uveal melanoma with Ru-106 plaque brachytherapy using COMS planning techniques, hypothesizing we would observe similar outcomes to those in the COMS.

**METHODS AND MATERIALS**—Medical records of patients undergoing Ru-106 plaque brachytherapy were reviewed retrospectively. Patient, tumor, and treatment characteristics were recorded. Outcomes including visual acuity, local tumor recurrence, salvage treatment, metastasis and survival were recorded. Cox regression analyses were used to determine factors associated with local tumor recurrence and enucleation.

**RESULTS**—Twenty-eight patients were studied. Median age was 60 and 50% were men. Median tumor base diameter and height were 9.4 and 2.6 mm. Ophthalmic complications were rare. Local tumor recurrence and enucleation occurred in 13 and 4 patients, respectively. Local tumor recurrence was associated with low visual acuity in the tumor-bearing eye, posterior tumors, small plaque size, and difference in plaque-tumor diameter <6 mm. Enucleation was associated with low visual acuity and posteriorly located tumor. Estimated 5-year rate of death and metastasis was 18.5% and 11.4%.

**CONCLUSIONS**—Among patients treated with Ru-106 plaque brachytherapy using COMS planning techniques, we found a greater than expected rate of local tumor recurrence. Planning Ru-106 plaque brachytherapy should be done carefully at centers that have previously used COMS protocols and I-125.

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#### **Keywords**

Ru-106; I-125; eye plaque; plaque brachytherapy; uveal melanoma; cancer; choroid; radiation

#### Introduction

Plaque brachytherapy is widely accepted as an effective treatment for uveal melanoma. Prospective trials have demonstrated that plaque brachytherapy is able to control growth of the primary tumor while conserving the eye and preserving useful vision (1, 2). The Collaborative Ocular Melanoma Study (COMS), a prospective randomized trial, found no difference in the survival of patients treated with plaque brachytherapy or enucleation of the eye (1). For this reason, plaque brachytherapy is an acceptable option for treatment of localized uveal melanoma. When treatment is recommended, most patients in the United States choose some form of radiation therapy as primary therapy of their uveal melanoma.

Although Co-60 was the original isotope used worldwide for more than 30 years, most prospective studies of plaque brachytherapy for uveal melanoma have used I-125 (or much less often Pd-103), despite the availability of many other radioisotopes for treatment (1–3).

Ru-106 has and continues to be used extensively in Europe. Theoretical advantages of Ru-106 plaques include a thin profile that facilitates placement, as well as the limited depth of penetration by the emitted beta-particles. The latter factor has lead most to consider Ru-106 appropriate for melanomas less than 5 mm high. Ru-106 has been unavailable in the United States for the last 5 years, but has recently been re-released for use.

During the brief period of time that Ru-106 was available for ophthalmic brachytherapy in the United States, we used this isotope for treatment of select patients with uveal melanomas less than 5 mm high. We used brachytherapy planning protocols similar to what is used for I-125. Given the re-release of this Ru-106 in the United States, we sought to review our experience and treatment outcomes. We hypothesized that the outcome of treatment would be similar to reports from other centers, and similar to the outcomes from the COMS trials. As a result of our findings we undertook an in-depth analysis of factors associated with outcome.

#### **Methods**

#### **Patients**

This retrospective clinical research study was carried out with permission from the institutional review board (WA0380-12) of Memorial Sloan Kettering Cancer Center. Patients with uveal melanoma 5 mm high treated with Ru-106 brachytherapy at our institution were identified through review of the brachytherapy treatment-planning databases.

Patient and tumor characteristics analyzed included age at diagnosis, visual acuity, intraocular pressure, tumor size (largest base diameter and height), shape (dome, collar button, placoid), uveal location (ciliary body and/or choroid), anterior border (ciliary body,

ora serrata to equator, posterior to equator), posterior border (ora serrata to equator or posterior to equator), distance to avascular fovea and optic nerve, and whether retinal detachment was present. Tumors were staged according to the COMS and American Joint Committee on Cancer (AJCC) criteria.

Treatment parameters were recorded, including BEBIG (Eckert & Ziegler Bebig s.a., Brussels, Belgium) Ru-106 ophthalmic applicator model (CCA, CIA, CIB, CCX), prescribed radiation dose (75–85 Gy to the apex of the tumor without a minimum or maximum dose to the sclera, based on our experience with I-125) and delivered radiation dose (to tumor apex and sclera surface), duration of brachytherapy, and use of adjuvant transpupillary thermotherapy (TTT, at the time of plaque removal, and/or 3–6 months after removal).

The outcome of treatment was recorded and included time from the end of brachytherapy to visual acuity <20/200, local tumor recurrence, salvage local therapy (TTT, photodynamic therapy, proton radiotherapy, and/or enucleation), melanoma metastasis, and death from melanoma or other cause. Local tumor recurrence events were independently reviewed and agreed upon by a radiation oncologist and an ophthalmic oncologist and were based on the COMS criteria (15% increase in height or 250 micrometer increase in tumor boundary on two consecutive occasions). Tumor region of the recurrence (horizontal/tumor margin, vertical/diffuse) was noted. Reason for enucleation and pathologic findings were noted. Visual acuity and intraocular pressure at last follow-up were recorded.

#### Statistical analysis

Summary statistics are presented. Kaplan-Meier methods were used to estimate rates of local recurrence, enucleation, metastasis, and death. Univariable Cox regression analyses of factors associated with local recurrence and enucleation are presented. Multivariable analyses were not undertaken because of the small sample size. All analyses were performed using WinSTAT for Excel® (version 2009.1; Microsoft Corporation, Redmond, WA) and figures were created with GraphPad Prism® software, version 6.02 (GraphPad Software, Inc., La Jolla, CA).

#### Results

Twenty-eight patients underwent Ru-106 plaque brachytherapy between 2000 and 2008 as their first treatment for uveal melanoma. There were 14 men and 14 women. Median age was 60 years (range, 28–82). Median tumor largest base diameter and height were 9.4 and 2.6 mm, respectively (range, 5.8–12.0 and 1.5–3.9, respectively). Median prescription and delivered radiation dose at tumor apex was 75.0 and 75.5 Gy, respectively (range, 75–85 and 66.8–89.3, respectively). Median radiation dose to the sclera surface was 238.7 Gy (range, 181.7–372.5). Median follow-up was 71 months (range, 10–95). Twelve patients harbored tumors meeting criteria for COMS small size, while 16 met criteria for medium size. T-staging by AJCC was T1a in 20, T1b in 4, and T2a in 4; no patients had clinical evidence of nodal or metastatic disease at diagnosis. Demographic, ophthalmic, tumor, and treatment characteristics are presented in Table 1.

Ophthalmic complications after treatment were rare. No patient developed neovascular glaucoma. Among 24 patients retaining the treated eye, 8 (33.3%) developed significant vision loss (acuity <20/200). In all but one of these patients, vision loss occurred after local tumor recurrence and additional local therapy. Therefore, preservation of vision (acuity 20/200) was 93.3% among patients without recurrence not undergoing additional local therapy. No patient required enucleation for ophthalmic complications.

Local tumor recurrence was more common than expected. Figure 1 depicts the probability of local recurrence and enucleation after brachytherapy. Thirteen (46.4%) patients were found to have local tumor recurrence after brachytherapy. In 8 (61.5%) patients recurrence was horizontal/marginal and in 5 (38.5%) patients the recurrence was vertical/diffuse. All patients underwent salvage therapy, with modalities presented in Table 2. Among 13 patients with tumor growth, 4 underwent enucleation, 10 underwent TTT, 2 underwent photodynamic therapy, and 1 underwent reirradiation with protons; some patients underwent more than one salvage therapy. In all patients that underwent enucleation, viable melanoma was found on histopathologic analysis.

Because of the high frequency of local treatment failure, further analysis was carried out to determine if any factors were associated with this event. Table 1 presents the characteristics, tumors, and treatment of patients that experienced local tumor recurrence and enucleation and those who did not. Five years after treatment, the estimated risks of local recurrence and enucleation were 41.5% (95% confidence interval [CI], 20.2–61.7%) and 16% (95% CI, 0.7–31.3%), respectively.

When the variables presented in Table 1 were tested in a univariable Cox regression model, six were found to be significantly associated with local tumor recurrence: low visual acuity in eye with tumor (HR, 2.4; 95% CI, 1.7–3.1; p=0.02), tumor close to the proximal edge of the optic disc (HR, 2.4; 95% CI, 1.5–2.4; p=0.005), tumor close to the center of the foveal avascular zone (HR, 2.1; 95% CI, 1.7–2.5; p=0.0001), posterior tumor border close to posterior pole (HR, 4.8; 95% CI, 3.6–6.0; p=0.009), smaller plaque size (HR, 3.6; 95% CI, 2.4–4.8; p=0.04), and difference in plaque diameter and tumor largest base diameter <6 mm (HR, 6.2; 95% CI, 4.7–7.8; p=0.02). When the variables in Table 3 were tested in a univariable Cox regression model, three were found to be significantly associated with enucleation: low visual acuity in eye with tumor (HR, 4.1; 95% CI, 2.9–5.2; p=0.02), low visual acuity in fellow eye (HR, 11.2; 95% CI, 8.8–13.5; p=0.04), and tumor close to center of foveal avascular zone (HR, 3.2; 95% CI, 2.2–4.2; p=0.02). Notably, gender, age, tumor apical height and longest basal dimension, location of posterior border, retinal detachment over tumor, tumor shape, radiation dose at tumor apex and sclera, plaque serial number, and adjuvant TTT were not associated with local tumor recurrence or enucleation.

The 5-year estimated rates of death and metastasis were 18.5% (95% CI, 1.6–49.3%) and 11.4% (95% CI, 0.1–49.7%).

#### **Discussion**

This study was designed to assess the outcome of Ru-106 plaque brachytherapy in patients with uveal melanoma. We found that treatment was well tolerated and ophthalmic complications were infrequent. However, we also found a high frequency of local tumor recurrence necessitating additional local therapy. We found that local tumor recurrence was significantly more common in patients with worse visual acuity in the tumor-bearing eye, in patients with posteriorly located tumors (near to the optic nerve and avascular foveal zone), and in patients treated with smaller plaques, and when the difference between the plaque diameter and tumor diameter was <6 mm. We found that enucleation was significantly more common in patients with worse visual acuity in the tumor-bearing and fellow eye, and in patients with tumors near the avascular foveal zone. While some of these findings have been previously reported (4), for the first time we report that tumor-plaque margin <6 mm is associated with local tumor recurrence after Ru-106 plaque brachytherapy.

Previous studies of Ru-106 have generally shown very low rates of local tumor recurrence. Table 3 presents the three largest independent studies each reporting on over 400 patients treated with Ru-106 plaque brachytherapy. With a similar duration of follow-up as the present study, local treatment failure in these studies was 2–14%. These studies reported that tumor size (5, 6) and posterior location (7) may be associated with treatment failure. Our study did not recapitulate the former finding (likely because of a narrow range of tumor sizes), but did corroborate the latter finding. In the Liverpool series, the brachytherapy planning technique is reported; however, in the other series, details regarding the planning techniques are not indicated. Importantly, it appears that in previous studies the tumor apex received doses of radiation 33% higher than those in the present study. Within the present study we did not find an association between radiation dose and local tumor recurrence, however, given the considerable differences in local tumor recurrence rates between the present study and prior studies using a higher dose of radiation, a relationship between local tumor recurrence and radiation dose may exist.

The effect of radiation dose may be of particular importance when considering the differences in dose distribution between Ru-106 and I-125 plaques that we have based our brachytherapy planning techniques on. Investigators in Cleveland conducted a dosimetric comparison between I-125 and Ru-106 eye plaques. In this study, when using plaques of the same size (18 mm) and radiation doses prescribed to the same depth (3 or 5 mm), greater lateral constriction of isodoses at the edge of the plaque were observed with Ru-106. At some isodose levels this difference was up to 20%, suggesting that for similarly sized plaques, with radiation prescribed to the same distance from the plaque, the dose at the edge of the plaque could be considerably lower with Ru-106 compared with I-125 (8). The reason for this difference is in part because of the way the Ru-106 plaque is manufactured. Ru-106 plaques have no isotope along the edge of the plaque. This detail is important and should be kept in mind during brachytherapy planning.

While differences in radiation dose distribution from Ru-106 and I-125 plaques have been previously appreciated, never before have clinical outcomes suggested this factor is of importance. The present study is therefore novel, because of the demonstrated association

between higher rates of local tumor recurrence and narrow tumor-plaque edge margin. The clinical significance implication of a low radiation dose at the edge of the Ru-106 plaque is further substantiated by the observation that local treatment failure occurred most often at the periphery in most cases (61.5%). This observation supports the dosimetric observations described above, specifically that the dose at the edge of Ru-106 is lower than a similarly designed I-125 plaque. This suggests that brachytherapy planning protocols used for I-125 are not sufficient for Ru-106 plaque brachytherapy.

The present series suggests a higher rate of local tumor recurrence than observed with I-125 in the COMS, or other prospective studies. The 5-year rate of local tumor recurrence in the present study was 41.5% (95% CI, 20.2–61.7%), while in the COMS 5-year local tumor recurrence was 10.3% (95% CI, 8.0–13.2%) (4). Although comparison of outcomes between studies is problematic, the 95% CIs of the results of these datasets do not overlap, suggesting the differences in these results may be significant. Moreover, other groups have reported higher rates of failure with Ru-106, compared to I-125. In 1999, investigators in London reported on 140 patients with uveal melanoma treated with proton therapy or plaque brachytherapy using I-125 or Ru-106. These investigators observed a significantly higher rate of local tumor recurrence with Ru-106 (10.7%) compared with I-125 (4.2%) (9). Similarly, investigators in Philadelphia reported on 354 patients with uveal melanoma 8 mm thick treated with plaque brachytherapy. They observed a significantly higher risk of enucleation after brachytherapy with Ru-106, compared with I-125 (10). While the present study did not compare the outcome of patients treated with Ru-106 to those treated with I-125 because of the presence of selection bias, prior studies comparing outcomes of Ru-106 and I-125 brachytherapy have reported inferior outcomes with Ru-106. We speculate that centers (such as ours) may have observed higher rates of local tumor recurrence because the difference in dosimetry between Ru-106 and I-125 plaques was not accounted for during brachytherapy planning.

Our study has several potential limitations. First, the retrospective nature of the design limits the quality of the data gathered. However, detailed clinical records have been maintained at our center for many years, and the major endpoints studied here are unlikely to have been affected because of the study design. Second, the cohort is small. As Ru-106 was only available in the United States for a few years, it is likely that the present study is one of the larger cohorts of patients treated in the United States, where most physicians plan ophthalmic brachytherapy based on techniques developed in the COMS using I-125. It is possible that our outcomes could be related to the early and limited use of Ru-106 at our center. The present contribution is important to the field because it emphasizes the need to adapt to the nuances of brachytherapy using Ru-106 in ophthalmic brachytherapy, and not to rely on treatment-planning methods used with other isotopes.

#### Acknowledgements

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#### **Glossary**

COMS Collaborative Ocular Melanoma Study

AJCC American Joint Committee on Cancer

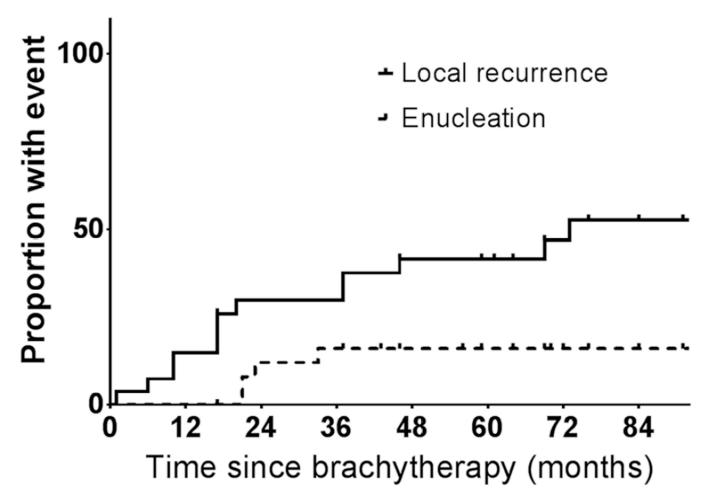
TTT transpupillary

CI confidence interval

**HR** hazard ratio

In conclusion, our study was designed to ascertain the outcome of Ru-106 in patients with uveal melanoma. We found that ophthalmic complications were infrequent, but local tumor recurrence was more common than expected. We found that posteriorly located tumors are more likely to recur after brachytherapy, as previously reported. For the first time, we report that the difference in size between tumor diameter and plaque diameter is associated with local tumor recurrence. As a modifiable factor in Ru-106 plaque brachytherapy, we encourage others to pay close attention to this factor when using Ru-106 plaques. The results suggest that margins used with I-125 cannot be applied to Ru-106 plaques, and as a result we will now adopt a strategy of 3 mm margins around the tumor when selecting the appropriate Ru-106 plaque, for a dose of 85 Gy at the tumor apex. An alternative approach would be to prescribe higher tumor apex doses to account for lateral dose constriction with this isotope, as has been done in European centers. Further study will be necessary to determine the optimal planning technique to maximize local tumor control and minimize ophthalmic complications.

## Local recurrence and enucleation



**Fig. 1.** Local recurrence and enucleation after Ru-106 brachytherapy for uveal melanoma.

### **Death and metastasis**

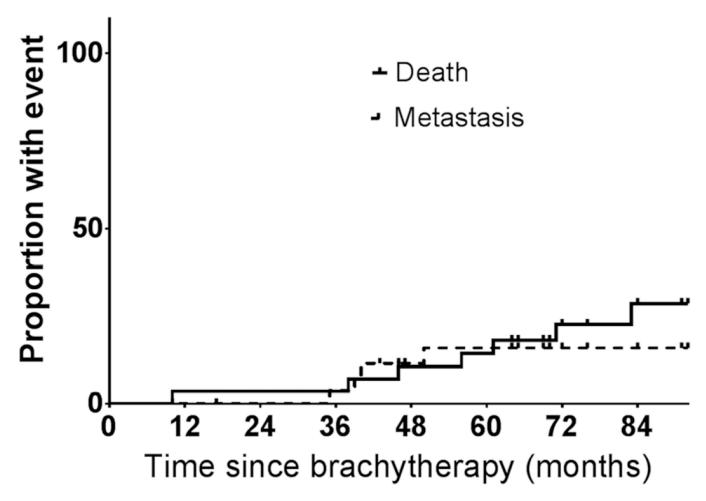


Fig. 2. Death and metastasis after Ru-106 brachytherapy for uveal melanoma.

Table 1

Demographic, ophthalmic, tumor and treatment characteristics with proportions of patients experiencing local tumor recurrence and enucleation among the cohort studied

			recur	recurrence		Enuc	Enucleation	
	Z		Yes	No		Yes	No	
Demographic characteristics								
Gender								
Male	14	20%	6	ď	64.3%	3	11	21%
Female	14	20%	4	10	28.6%	_	13	%L
Age (years)								
<50	v	18%	8	2	%0.09	-	4	20%
9-09	14	%09	7	7	50.0%	3	11	21%
70	6	32%	8	9	33.3%	0	6	%0
Ophthalmic characteristics								
Visual acuity in eye with tumor								
20/20	1	4%	0	-	0.0%	0	_	%0
20/25-20/40	19	%89	∞	11	42.1%	1	18	2%
20/50-20/160	S	18%	2	3	40.0%	-	4	20%
20/200	8	11%	8	0	100.0%	2	-	%19
Visual acuity in fellow eye								
20/20	2	7%	1	1	50.0%	0	2	%0
20/25-20/40	25	%68	11	14	44.0%	3	22	12%
20/50–20/160	1	4%	_	0	100.0%	_	0	100%
20/200	0	%0	0	0		0	0	
Tumor characteristics								
Tumor apical height (mm)								
<2.5	111	39%	9	5	54.5%	_	10	%6
2.5–5.0	17	61%	7	10	41.2%	8	14	18%
Longest basal dimension (mm)								
<4.5	0	%0	0	0	%0.0	0	0	%0

4.5-8.0									
4.5-8.0 8.1-11.0		Z		Yes	No		Yes	$N_0$	
8.1–11.0		5	18%	3	2	%0.09	1	4	20%
		41	20%	7	12	36.8%	2	17	11%
11.1–14.0	,	4	14%	33	-	75.0%	_	3	25%
Distance to proximal edge of optic disc (mm)	c (mm)								
<2		_	4%	_	0	100.0%	0	-	%0
2.1-4.0		7	25%	5	2	71.4%	3	4	43%
4.1–6.0		7	25%	5	2	71.4%	0	7	%0
6.1–8.0	,	4	14%	1	3	25.0%	-	3	25%
8<		6	32%	1	~	11.1%	0	6	%0
Distance to center of foveal avascular zone (mm)	zone (mm)								
0	,	4	14%	4	0	100.0%	2	2	20%
0.1–2.0	,	4	14%	2	2	80.0%	-	3	25%
2.1–5.0		33	11%	ж	0	100.0%	_	2	33%
5.1-8.0		9	21%	8	33	50.0%	0	9	%0
>8.0		_	39%	1	10	9.1%	0	11	%0
		_							
Location of anterior tumor border									
Ciliary body	,	4	14%	0	4	0.0%	0	4	%0
Equator to ora serrata		_	36%	8	7	30.0%	0	10	%0
		0							
Posterior to equator		_	%09	10	4	71.4%	4	10	29%
	,	4							
Location of posterior tumor border									
Equator to ora serrata		_	4%	0	-	0.0%	0	_	%0
Posterior to equator		2	<b>%96</b>	13	14	48.1%	4	23	15%
	`	7							
Retina detached over tumor									
No		2	82%	6	14	39.1%	2	21	%6
		3							

			Local	Local tumor recurrence		Enucl	Enucleation	
	Z		Yes	No		Yes	N <sub>o</sub>	
Yes	5	18%	4	-	80.0%	2	ю	40%
Tumor shape								
Dome	2	%68	11	14	44.0%	4	21	16%
	5							
Collar button	-	4%	-	0	100.0%	0	1	%0
Placoid	2	7%	-	1	50.0%	0	2	%0
<u>Treatment characteristics</u>								
Delivered dose at tumor apex (Gy)								
65.0–80.0	-	%89	7	12	36.8%	2	17	11%
	6							
80.1–85.0	7	25%	5	2	71.4%	-	9	14%
85.1–90.0	2	7%	-	1	50.0%	1	1	20%
Delivered dose to sclera (Gy)								
<293.0	2	%6 <i>L</i>	11	111	50.0%	2	20	%6
	7							
293.0–342.9	2	7%	_	_	50.0%	-	_	20%
343.0–409.9	4	14%	_	3	25.0%	1	8	25%
410	0	%0	0	0	%0.0	0	0	%0
Plaque model (physical diameter, active diameter in mm)								
CCX (11.6, 9.5)	_	4%	_	0	100.0%	0	-	%0
CCA (15.3, 13.0)	2	%62	12	10	54.5%	4	18	18%
	2							
CIA (15.3, 13.0)	$^{\circ}$	11%	0	ю	%0.0	0	ю	%0
CIB (20.2, 17.8)	2	%/	0	2	%0.0	0	2	%0
Plaque serial number								
CCX-104	_	4%	_	0	100.0%	0	_	%0
CCA-571	6	32%	5	4	55.6%	-	∞	11%
CCA-992	-	39%	2	9	45.5%	7	6	18%
	-							

			Local tumo recurrence	Local tumor recurrence		Enucleation	eation	
	Z		Yes	No		Yes	N <sub>0</sub>	
CCA-892	2	7%	2	0	100.0%	-	-	20%
CIA-173	7	%/	0	2	%0.0	0	2	%0
CIA-156	-	4%	0	-	%0.0	0	_	%0
CIB-307	2	%/	0	2	0.0%	0	2	%0
Difference in plaque diameter and tumor largest base diameter	neter							
e mm 9>	-	21%	10	9	62.5%	33	13	19%
	9							
6 mm	_	43%	33	6	25.0%	-	11	%8
	2							
Adjuvant transpupillary thermotherapy								
Yes	∞	29%	2	9	25.0%	-	7	13%
No	2	71%	11	6	55.0%	ю	17	15%
	0							

Table 2

Salvage therapy after local tumor recurrence with Ru-106 brachytherapy

Salvage local therapy*	N	%
Enucleation	4	14.3
Transpupillary thermotherapy	10	35.7
Photodynamic therapy	2	7.1
Proton therapy	1	3.6

 $<sup>^{*}</sup>$  Some patients underwent more than one salvage local therapy.

Table 3

Previously reported series of 400 patients treated with Ru-106 brachytherapy for uveal melanoma

Institution	Eyes treated (n=)	Treatment period (years)	Treatment Radiation dose period prescribed (years)	Radiation dose delivered	Planning margins	Median follow-up Local tumor Crude (months) recurrence recurre (n=) rate	Local tumor recurrence (n=)	Crude recurrence rate	Enucleated Crude (n=) enucles rate	Crude enucleation rate
St Erik's Eye Hospital, Stockholm	579	1979–2003	1979–2003 100 Gy to 1 mm beyond tumor apex	Median 100 Gy to tumor apex	Not reported	82 among living 55 among deceased	79	14%	106	18%
Royal Liverpool University Hospital	458	1993–2001	80–100 Gy to tumor apex; 300 Gy to sclera	Median 100–115 Gy to tumor apex; median 400–500 Gy to sclera	Median 100–115 Gy At least 2 mm around to tumor apex; tumor; 15.3 mm plaque median 400–500 Gy if tumor base diameter 10 mm plaque if tumor base diameter 10 mm	46.8	6	2%	8	2%
Leiden University Medical Centre	425	1993–2004	400–800 Gy to sclera	100–150 Gy to tumor apex	Not reported	50 for survivors	16	4%	17	4%
Present study	28	2000–2008	2000–2008 75–85 Gy to tumor apex	Median 75.5 Gy to tumor apex	At least 2 mm around tumor	71	13	46%	4	14%