

# Ruthenium-106 eye plaque brachytherapy in the conservative treatment of uveal melanoma: a mono-institutional experience

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**Abstract. – BACKGROUND:** Traditional treatment for uveal melanoma is the enucleation of the eye with outcomes cosmetically unacceptable and loss of useful vision. Plaque brachytherapy, compared to enucleation, had the advantage to preserve the eye with outcomes cosmetically acceptable and preservation of vision.

**PATIENTS AND METHODS:** From July 1990 to December 2009 one hundred forty-two (142) patients (51 males and 91 females) with small to medium uveal melanoma were treated with <sup>106</sup>Ru plaque brachytherapy. The patients underwent a complete staging before brachytherapy with indirect ophthalmoscopy and ultrasounds. Mean tumour thickness was 3.26 mm (1.6-6 mm). The dose scheduled was 80-100 Gy to the apex with a maximum dose of 800 Gy to the sclera.

**RESULTS:** One hundred forty-two have been treated, nine patients had lost the follow-up and drop out; 133 patients were assessed. Mean follow-up was 7.7 years (6 months-18 years). The overall survival at 5, 10 and 15 years was 92%, 85% and 78% respectively. Cancer free survival was 95%, 90% and 83%, respectively at 5, 10 and 15 year. Radiation-induced toxicity was represented in 47 patients with a 5 year actuarial survival rate free from complications of 54%.

**CONCLUSIONS:** <sup>106</sup>Ru plaque brachytherapy is a valid approach for treatment of uveal melanoma. This technique is efficacy and safe, with a low toxicity profile.

*Key Words:*

Uveal melanoma, Ocular brachytherapy, Ruthenium.

## Introduction

Uveal melanoma represents about 5% of all melanomas<sup>1</sup>. Traditional treatment has been enu-

cleation. Conserving approach has been developed with the aim of preserving vision without increasing the risk of metastatic spread<sup>2</sup>.

Nowadays, ruthenium-106 (Ru-106) or iodine-125 plaque brachytherapy, proton beam radiotherapy, stereotactic radiotherapy, local resection, and phototherapy have demonstrated to be useful to treat uveal melanoma and could represent standard of treatment.

In 1991 the Collaborative Ocular Melanoma Study<sup>3</sup> demonstrated the efficacy of plaque brachytherapy in a multicenter randomised trial which did not show any difference between enucleation and I-125 brachytherapy in 5 years survival and in 5 years rates of death with melanoma metastases. Furthermore, brachytherapy made it possible to focus on the preservation of useful vision, cosmetic appearance and quality of life as well.

In this study, we present our caseload with <sup>106</sup>Ru plaque brachytherapy showing the values of local control and survival after brachytherapy and related to radiation-induced toxicity.

## Patients and Methods

A retrospective review was undertaken on patients with uveal melanomas, treated with <sup>106</sup>Ru plaque brachytherapy from July 1990 to December 2009. One hundred forty-two patients (51 males and 91 females) with small to medium uveal melanoma were treated with <sup>106</sup>Ru plaque brachytherapy at the University Hospital of Ferrara, Italy.

The diagnosis of uveal melanoma was based on ophthalmoscopic and ultrasonographic findings and fluorescein angiography. The tumour size

was classified according to the Collaborative Ocular Melanoma Study (COMS) criteria<sup>3,4</sup> and TNM Staging System<sup>5</sup>.

Patients were eligible for Ru-106 brachytherapy if they had a small or intermediate size melanoma (basal diameter up to 16.50 mm and tumour prominence up to 6 mm). At time of diagnosis, all patients were evaluated by liver ultrasonography, chest radiography and routine blood tests.

All patients were treated with commercially available Ru-106/Rh-106 applicator, manufactured by Bebig GmbH (Berlin, Germany). Tumour margins were demarcated intraoperatively using indirect ophthalmoscopy and transillumination. Tumour received at least a 2 mm safety margin.

The brachytherapy dose was prescribed at the scleral surface and standardized to a dose rate of 100 Gy at the apex. Ruthenium plaques were subsequently positioned and left in place until the prescribed treatment dose had been delivered to the tumour apex (mean time: 3 days and 16 hours).

After irradiation, follow-up were conducted 1 month after treatment, at 3-month intervals for 2 years, then twice a year until 5 postoperative years and then annually. Follow-up examinations included ophthalmoscopy, ultrasonography and, if necessary, fluorangiography. Visual acuity was assessed by decimal values.

Outcome measures were: overall survival and cancer free survival, local recurrence and distant metastases. A local recurrence was defined as insufficient tumour regression with signs of tumour activity on fluorescein angiography, or documented tumour growth. Instead, tumour control was defined as a flat scar or a regressed lesion not showing any signs of tumour activity.

Complications such as retinopathy, maculopathy, optic neuropathy, retinal haemorrhage and exudative retinal detachment were evaluated at each follow-up.

Follow-up time was calculated from first day of brachytherapy to date of last information on vital status. Time intervals to death, to local recurrence or metastases and to complications were calculated from the first day of brachytherapy to the date of death or diagnosis of recurrence or complication, with censoring at date of last contact.

### **Statistical Analysis**

Kaplan-Meier method was used to estimate all endpoints. Differences in the survival rate were assessed by the long-rank test<sup>6</sup>. The Cox model was used to identify the risk factors for overall

survival<sup>7</sup>. The following variables at baseline were considered for survival univariate analysis: sex, age, tumour diameter, tumor height and enucleation.  $p < 0.05$  was considered statistically significant.

## **Results**

### **Features of Patients at Baseline**

Our study group consisted of 51 men (35.9%) and 91 women (64.1%). The 142 patients ranged in age from 29 years to 87 years (mean 62.1 years) at the time of treatment. Visual acuity at baseline examination ranged from  $< 1/10$  to 10/10 (median 7/10) in the 142 study eyes. The 142 tumors ranged from 1.6 to 6 mm in thickness (mean 3.26 mm) and from 7 to 16.50 mm in largest basal diameter (mean 10.5 mm). The tumors were classified according to the TNM system<sup>5</sup> as T1 in 63 eyes (44.4%), T2 in 76 eyes (53.5%), and T3 in 3 eyes (2.1%).

According to the COMS system<sup>3,4</sup> the tumors were small in 62 eyes (43.7%) and medium in 80 eyes (56.3%). The centre of the tumor lay posterior to the equator in 93 eyes (65.5%), between the equator and ora serrata in 49 eyes (34.50%). No tumor lay anterior to the ora serrata in the ciliary body. Patient demographics, tumour and treatment characteristics are summarized in Table I.

### **Follow-up**

The mean length of follow-up after brachytherapy was 9.8 years (median 9.8 years, range 9.8-232.8 months) for all the patients. Nine was lost at follow-up visits, afterwards 133 patients have been assessed. During follow-up, a total of 18 deaths occurred. Death due to cancer occurred in 8 patients (6.1%) for metastatic spread.

The actuarial overall survival rates at 5, 10 and 15 years was 92%, 85% and 78% respectively (Figure 1).

Survival was longer among patients younger than 70 years ( $p = 0.0025$ ). No other variable was related to survival. Cancer-free survival was 95%, 90% and 83% at, respectively, 5, 10 and 15 years (Figure 2).

Thirty-three patients (24.8 %) experienced tumor progression: 23 patients (17.3%) experienced local tumor progression and 8 (6%) distant metastases (liver and brain). The mean time to progression was 66 months. Local recurrence free survival at 5, 10 and 15 years was 85%, 79% 76% (Figure 3).

**Table I.** Tumor characteristics at diagnosis on 142 consecutive patients treated with ruthenium-106 brachytherapy for uveal melanoma.

	No.	%
Age (yrs)		
20-30	2	1.4
31-40	10	7
41-50	14	9.9
51-60	31	21.8
61-70	48	33.8
> 70	37	26.1
Median	64.5	
Gender		
Male	51	35.9
Female	91	64.1
Laterality		
Right	76	53.5
Left	66	46.5
Tumor Location		
Central	26	18.3
Para-central	67	47.2
Peripheral	49	34.5
T Stage		
1	63	44.4
2	76	53.5
3	3	2.1
Height (mm)		
≤ 3	66	46.5
> 3 ≤ 5	66	46.5
> 5	10	7
Largest basal diameter (mm)		
≤ 10	46	32.4
> 10 ≤ 15	89	62.7
> 15	7	4.9

All 23 patients with a local recurrence had received an active treatment (8 retreated with ruthenium plaques, 10 with enucleation, 2 with proton therapy, and 3 with transpupillar thermotherapy), all patients were alive and disease free.

**Treatment Safety**

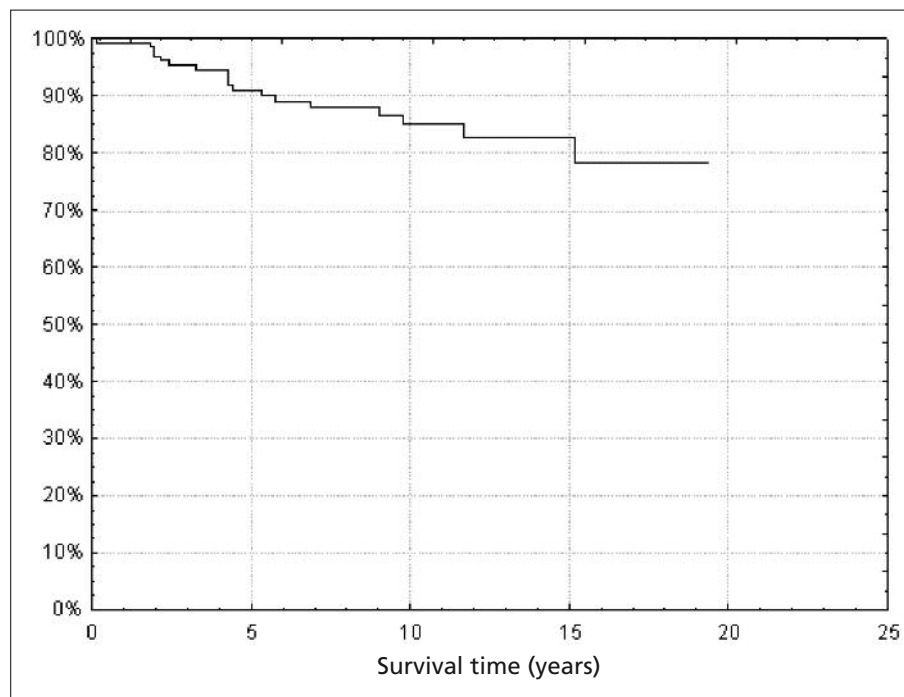
The acute toxicity was principally related to the surgical procedure and resolved with medical treatment. Instead, 47 patients developed ocular complications, resulting in a 5 year actuarial survival rate free from complications of 54%. Thirty-two patients had radiation complications such as retinopathy (n = 32), maculopathy (n = 20) and combinations of these (n = 2).

No case of dries eyes or neo-vascular glaucoma was recorded. No enucleation due to side effect like pain, neovascular glaucoma or an unsightly eye.

Sixty-two patients experimented a subconjunctival pigmentation in irradiated area. Histological examinations of these spots showed pigment-loaded macrophages and no sign of extrascleral tumor extension.

**Analysis of Visual Acuity**

The visual acuity was checked at every control during the follow up. We report a summary in Table II of all follow up, showing the visual acuity score at 1, 3, 5, 7, 10 and 15 years.



**Figure 1.** Overall survival.

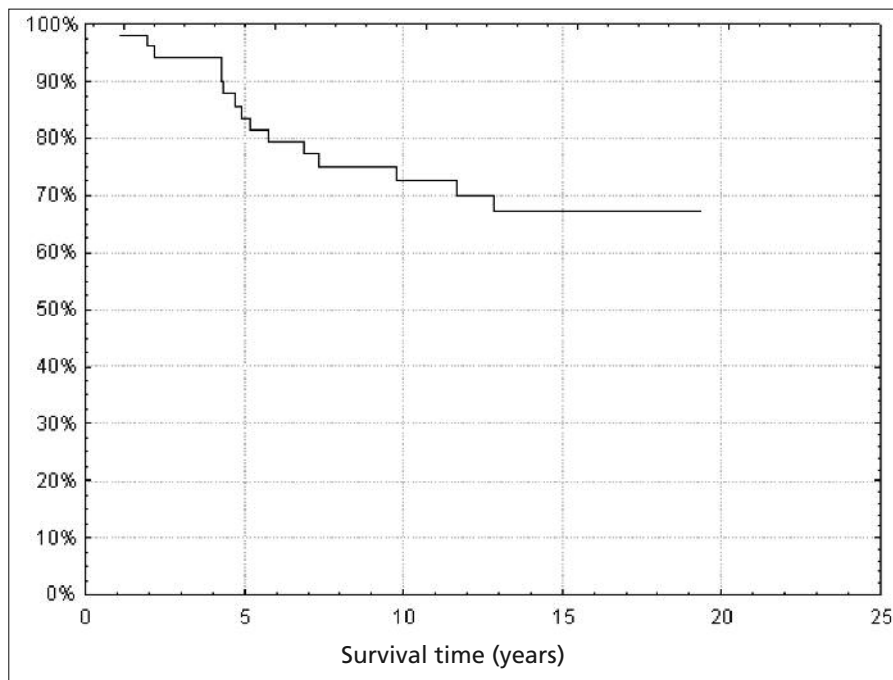


Figure 2. Cancer free survival.

### Discussion

Brachytherapy is a well recognized method to treat conservatively ocular melanoma. A randomized clinical trial has evidenced no clinically or statistically meaningful differences in overall survival rates (43% vs. 41%, respectively) or death with histopathologically confirmed melanoma metastasis (21% and 17%, respectively) between treatment arms comparing brachytherapy with enucleation for up to 12 years after treatment<sup>3</sup>. Furthermore, it is demonstrated the efficacy of brachytherapy to achieve sustained local tumor control, to conserve the globe and to not increase the risk of distant metastases. Based on the COMS trial conclusion, brachytherapy with 125-I plaques is considered the standard approach to

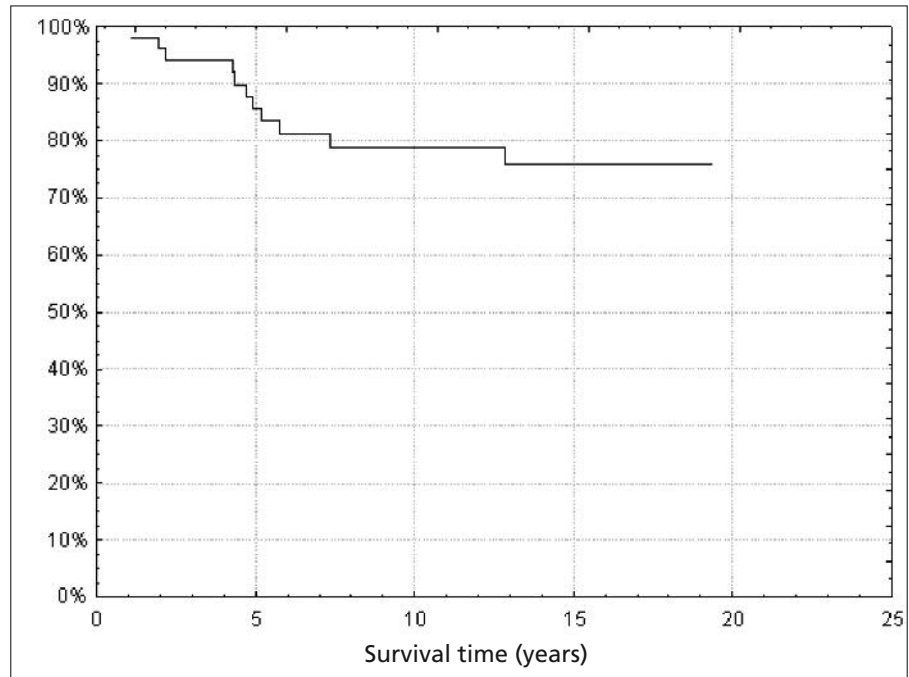
uveal melanoma. Unfortunately, brachytherapy is associated with significant visual loss secondary to radiation complications<sup>8,9</sup>. Radiation optic neuropathy and radiation retinopathy are two visually significant complications that are currently untreatable. Therefore, it's necessary decrease the rate of these side effects.

Another radioisotope used to treat uveal melanoma is ruthenium. A lot of studies have demonstrated the possibility to use it for eye-conserving treatment, obtaining a tumour control rate of more than 95%, with a careful selection of cases. A recent dosimetric study<sup>10</sup> demonstrates that ruthenium could be superior to iodine plaques in sparing normal structures such as the lens, macula and optic disc and so in decreasing side effects.

Table II. Tumor characteristics at diagnosis on 142 consecutive patients treated with ruthenium-106 brachytherapy for uveal melanoma.

	Patients No.	BCVA 6-10/10 No. (%)	BCVA 3-5/10 No. (%)	BCVA 1-2/10 No. (%)	BCVA < 1/10 No. (%)
Baseline	142	89 (62.67)	35 (24.64)	9 (6.33)	9 (6.33)
1 year	129	88 (68.21)	18 (13.90)	9 (6.97)	14 (10.80)
3 years	113	72 (63.7)	22 (19.5)	7 (6.2)	12 (10.6)
5 years	91	45 (49.45)	21 (16.20)	14 (15.38)	11 (12.08)
10 years	50	17 (34)	11 (22)	9 (18)	13 (26)
15 years	14	5 (35.71)	1 (7.14)	3 (21.42)	5 (37.71)

**Figure 3.** Local recurrence free survival.



The aim of the present study was to analyze our caseload in the use of Ruthenium plaque brachytherapy routinely applied in uveal melanoma patients.

Twenty-three patients (17.3%) experienced local recurrence. This is a high rate of recurrence treating small and medium-sized tumors in comparison to other published reports. Although comparing local control rates between different institutions may not be reliable, as there is considerable inter-study variation and case mix differences, we have analyzed critically the local recurrence. Thirteen (9.8%) are occurred in patients treated in initial training period and are related with geometrical and dosimetric errors. Excluding these local recurrences, however re-treated with excellent results, the remaining ten (7.5%) are probably related to tumor aggressiveness. In order to avoid selection bias that hampered retrospective studies, we reported globally our experience. Eight (34.8%) patients were re-treated with ruthenium plaques, 10 (43.5%) with enucleation, 2 (8.7%) with proton therapy, and 3 (13%) with transpupillar thermotherapy.

Globally, overall and cancer-free survival rates were respectively 92%, 85% and 78% and 95%, 90% and 83% at 5, 10 and 15 years. These data are comparable to those referred by other groups for small or medium sized melanomas and confirm that eye-conserving treatment does not impair survival.

A disappointing finding of this radiation treatment is the deterioration in visual acuity from retinopathy, maculopathy, opticopathy and other ocular side effects.

In COMS trial<sup>3</sup> Authors reported that a 43% of their treated eyes at 3 years had a visual acuity 20/200 or worse using iodine plaques. In our study, at 3 years, 83.2% of patients had a visual acuity  $\geq$  5/10. A worsening of visus appears late in the follow-up, at 10 years 56% of patients had a visual acuity  $\geq$  5/10, this fact could be related to the aging and cataract genesis. This high rate  $\geq$  5/10 visual acuity could be related to low incidence of radio-induced late toxicity as retinopathy or maculopathy.

Furthermore, there is no patient experimented sclera necrosis, neovascular glaucoma or non resolving vitreous haemorrhage.

These data could confirm the advantage of ruthenium brachytherapy over iodine when assessing the risks for radiation injury.

**Table III.** Toxicity of 133 consecutive eyes treated with ruthenium-106 brachytherapy for uveal melanoma.

	No.	%
Retinopathy	32	24.1
Cataract	20	15
Maculopathy	3	2.2
Papillopathy	3	2.2

We have not observed enucleation caused by ocular side effects unlike previous series where 20-30% of enucleation were caused by toxicity<sup>10,11,20,23</sup>; probably because of small dimensions the tumor and the relatively low dose used and administered to the apex and to the sclera.

### Conclusions

Looking to all data of our series, we can conclude that ruthenium-106 eye plaque brachytherapy permitted to obtain a good survival in patients with small and medium-size uveal melanoma and a good quality of life with an acceptable toxicity.

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