

Original Article

# Characteristics, management, and outcome of patients with uveal melanoma treated by Iodine-125 radioactive plaque therapy in a single tertiary cancer center in Jordan



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## Abstract

**Objective:** To evaluate King Hussein Cancer Center experience in using Iodine-125 COMS radioactive plaque for treatment of Uveal Melanoma in Jordan.

**Methods:** Retrospective case series of eyes with uveal melanoma treated by Iodine-125 COMS radioactive plaque therapy. Data collection required access to medical, radiology, Labs and pathology reports. Main outcomes studied includes: Demographics, tumor features, eye salvage, visual outcome, metastasis, and mortality.

**Results:** Between September 2008 and March 2015, 28 eyes for 28 patients had intraocular uveal melanoma and treated by Iodine-125 radioactive plaque therapy. The mean age at diagnosis was 48 years and 16(57%) were males. The mean tumor thickness was 8 mm (range: 4–13 mm), and 27(96%) patients had medium or large size tumor. The radioactive plaques used had a median size of 16 mm (range: 12–20 mm). The mean apical dose was 83.5 Gy (range 81–87 Gy), and the median radiation rate was 7.25 (range: 4.5–13). At median follow up of 2 years (range 0.5–7 years), eye salvage rate was 93%. Four (15%) patients had distance metastasis, and 3(11%) were dead. Fifty percent of patient had visual acuity better than 20/200 at the last date of follow up.

**Conclusion:** Our preliminary results are encouraging and are comparable to another countries worldwide. The use of Iodine-125 COMs plaque therapy at the inspection of implementation of plaque therapy in the developing countries can lead to eye salvage in more than 90% of cases, and reserves functional vision in more than 50% of cases.

**Keywords:** Choroid, Enucleation, Melanoma, Radioactive plaque therapy

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## Introduction

Uveal melanoma is the most common primary intraocular malignancy in adults and accounts for 5% of all melanomas.<sup>1</sup> It is seen more frequently in Caucasians in comparison with Hispanics, Asians and Africans. For the Whites in the United States, uveal melanoma has an incidence of 0.69 and 0.54

per 100,000 person-year for males and females consecutively with a mean age of 60.<sup>1</sup>

Uveal melanoma mostly appears in the choroid (85–91% of cases), and it is localized to the ciliary body or the iris in 9–15% of cases.<sup>2</sup> Iris melanomas are associated with the earliest detection and overall best prognosis<sup>3</sup> while ciliary body melanomas are associated with the worst prognosis.<sup>4</sup> Around

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50% of patients diagnosed with uveal melanoma will develop metastasis, despite treatment, with survival time after metastasis averaging 6–12 months.<sup>5,6</sup>

The Collaborative Ocular Melanoma Study (COMS) concluded that there was no significant difference between brachytherapy and enucleation in terms of prevention of metastasis and mortality for medium sized melanomas,<sup>7,8</sup> therefore, globe and vision-preserving radiation therapy is the primary treatment of choice for most of uveal melanomas nowadays in the developed world.<sup>1</sup>

Prior to introduction of plaque therapy, patients with the diagnosis of Uveal melanoma underwent enucleation as primary form of treatment at the cost of saving life but scarifying globe and loss of vision. While with the introduction of plaque therapy, it has revolutionized the management and resulted in greater cosmetic effect, preservation of globe and saving some vision in selected case and saving life.<sup>8</sup> In Jordan before 2008, all patients with Uveal melanoma underwent enucleation, but after establishing Plaque therapy program at king Hussein cancer center, plaque therapy has been employed at our center since 2008.<sup>9,10</sup> We report our experience with Iodine-125 (I-125) COMS plaque in our patients with uveal melanoma.

## Patients and methods

This study was approved by the Institutional Review Board in KHCC. It was a retrospective case series of 28 eyes of 28 consecutive patients from September 2008 to January 2015 who had intraocular uveal melanoma and treated by Iodine-125 (I-125) radioactive plaque. Selection required access to patients' medical charts, pathologic records, radiology reports, and Labs.

Outcome measures included: patient's age at diagnosis, gender, laterality, smoking, presenting symptoms and visual acuity at presentation. Evaluated tumor clinical characteristics included: tumor location, surface features, shape, thickness, largest basal diameter, size, pigmentation, presence of subretinal fluid, vitreous hemorrhage, cataract, neovascular glaucoma, rubeosis, MRI features, TNM staging, presence and site of metastasis, plaque size, apex dose, rate of radiation, distance between tumor's edge and the optic nerve and the fovea, tumor thickness and visual acuity after treatment.

## Inclusion and exclusion criteria

The eligibility criteria for inclusion were eyes with clinical diagnosis of intraocular uveal melanoma treated by radioactive plaques. Radioactive plaque was not used for melanomas involving or touching the optic nerve, thicker than 15 mm, associated with total retinal detachment and/or secondary neovascular glaucoma (NVG), with extraocular extensions, and when the patient couldn't offer the cost of the plaque.

## Tumor characteristics and definitions

In this study, the tumors were classified according to the Collaborative Ocular Melanoma Study (COMS) classification. The COMS divided uveal melanomas based on size into small, medium and large tumors. Small melanoma; 5–16 mm at the largest basal diameter (LBD) and 1–3 mm in apical

height. Medium-sized melanoma; 16 mm or less at the LBD and had an apical height between 3 mm and 10 mm. And uveal melanomas more than 16.0 mm at the LBD and more than 10 mm in height were defined as large tumors. TNM staging was according to the 7th edition of the American Joint Committee on Cancer (AJCC) staging system.<sup>11</sup>

Follow-up of these patients was documented including period, evidence of metastasis and patient status during the period of the follow-up.

## Results

Seventy-six eyes were diagnosed with uveal melanoma in King Hussein Cancer Center (KHCC) between September 2008 and January 2015. Thirty patients were excluded from the data analysis because of inadequate data and/or refused treatment and were lost for follow up, and 28 patients were treated by I-125 radioactive plaque.

## Demographics and clinical features

28 eyes with uveal melanoma from 28 patients were studied. The mean age at diagnosis was 48 years (median 44 years, range; 21–75 years). There were 16(57%) males and all (100%) patients had single tumor. All of them were treated by I-125 radioactive plaque therapy, but 2 of them were consecutively enucleated. Demographics are in [Table 1](#).

## Tumor features

The melanoma was in the choroid in 23(82%) eyes, in the ciliary body in 5(18%) eyes, and no single patient had iris melanoma in this series. According to the 7th edition of the American Joint Committee on Cancer staging system (UICC/AJCC); 8(29%) were T1, 10(36%) were T2, 9(32%) were T3, and 1(3%) were T4. The median initial tumor thickness was 7.0 mm (mean 7, range 3–14 mm), and the median tumor base dimension was 10.5 mm (mean 11, range 7–16 mm). The distance between tumor margin and the fovea was (mean 4.7 mm, range; 0–16 mm), and between tumor margin and the optic disc was (mean 6.5 mm, range; 2–19 mm). Details of tumor features are in [Table 2](#).

**Table 1.** Demographics and clinical features.

Number		28	%
Age (Years)	Range	21–75	
	Median	44	
	Mean	48	
Gender	M	16	57
	F	12	43
Side	Right	11	39
	Left	17	61
Smoking	Yes	8	29
	No	20	71
Presenting symptom	Impaired vision	20	71
	Accidental	5	18
	Others <sup>a</sup>	3	11
Visual acuity at presentation	≥0.5	14	50
	0.1–0.4	9	32
	<0.1	5	18

<sup>a</sup> Others included: floaters, wondering eyes.

### Plaque features

The radioactive plaques used had a median size of 16 mm (range: 12–20 mm). The mean apical dose was 83.5 Gy (range 81–87 Gy). scleral dose ranged from 325 to 640 Gy, and the median radiation rate was 7.25 (range: 4.5–13). At last follow up after therapy, tumor thickness was <5 mm in 13(46%) eyes, and 5–10 mm in 13(46%) eyes. The median tumor thickness after therapy was 4.5 mm (range; 2–8 mm), and the decrease in tumor thickness was variable between the treated eyes (Table 3).

After therapy, visual acuity was equal or better than 0.5 in 11(42%)eyes, 0.1–0.4 in 5(19%) eyes, and less than 0.1 in 10 (38%)eyes. 2(7%)eyes had vision improvement while 15 (54%) eyes had vision worsening after treatment. The main complications included Cataract (5(18%) eyes), NVG (7(25%) eyes), recurrence (1(4%) eye), radiation optic neuropathy (1(4%) eye) and radiation retinopathy (5(4%) eyes).

### Outcome and follow up

At a median follow up of 24 months, 26(93%) eyes were salvaged while 2(7%) eyes have been enucleated; one for tumor recurrence, and one for uncontrolled painful NVG.

Four patients out of 28 patients (14%) included in our series had metastasis. One (3%) patient had lymph node metastasis (N1), and 3(11%) patients showed distant metastasis (M1) (3 patients had liver metastasis, 1 had lymph nodes metastasis and 1 had bone metastasis. No patient had the metastasis at time of diagnosis, but all of them were discovered to have metastasis after treatment by an average interval of 28 months (range 6–48 months). All the metastatic patients had the melanoma in the choroid. One was mushroom shape, and 3 were dome shape tumors. Two were T1, 1 was T3, and 1 was T4. Three were melanotic, and 1 was amelanotic tumor, and none of them had local tumor

**Table 2.** Tumor characteristics.

Number		28	%
Site	Choroid	23	82
	Ciliary body	5	18
	Iris	0	0
Shape	Dome	26	93
	Mushroom	2	7
Thickness at diagnosis	>10	4	14
	5–10	18	65
	<5	6	21
Largest basal diameter	<5	0	0
	5–16	28	100
	>16	0	0
Size	Small	1	4
	Medium	20	71
	Large	7	25
Pigmentation	Melanotic	26	93
	Amelanotic	2	7
T-stage	T1	8	29
	T2	10	36
	T3	9	32
	T4	1	3
Associated features <sup>a</sup>	Subretinal fluid	17	61
	Vitreous hemorrhage	5	18
	Glaucoma	2	7
	Cataract	5	18
	Orange Pigments	25	89

<sup>a</sup> Some patients have more than one associated feature.

**Table 3.** Final outcome.

Number		28	%
Change in Tumor thickness	<30%	10	36
	30–50%	9	32
	>50%	7	25
Change in Visual acuity	Stable	8	29
	Better	2	7
	Worse	15	54
Salvage	Yes	26	93
	No	2	7
Metastasis	Yes	4	15
	No	25	89
Alive	Yes	25	88
	No	3	11
F/U (y) <sup>a</sup>	Range	0.5–5	
	Median	2	
	Mean	2.18	

<sup>a</sup> Follow up period in years.

recurrence. Three of the patients with metastasis (11%) were dead at last date of follow up (Table 3).

### Discussion

King Hussein cancer center is a referral center for Plaque Therapy for Uveal Melanoma in Jordan, and the number of treated cases during the period of 2008–2015 provide the impression that the occurrence of Uveal Melanoma in Jordan is low. Similarly, in Saudi Arabia, one study showed only 40 cases of uveal melanoma diagnosed between 1983 and 2005, only 28 of them were of Saudi Arabian ancestry.<sup>12</sup> Similarly, another report from the Shanghai Eye, Ear, Nose and Throat Hospital in China showed only 103 cases of uveal melanoma diagnosed between 1955 and 1979.<sup>13</sup> Even statistics about the incidence of uveal melanoma in the middle east and most of the eastern and developing countries are missed, it seems that the incidence in the Middle East and in Asia is less than the incidence of uveal melanoma in USA and Europe.

Patients in our study presented at an average age of 46 years which is around 14 years less than the patients who participated in the Collaborative Ocular Melanoma Study (COMS).<sup>8</sup> In this series there was very slight non significant predominance of male over female (57% were male), while most of the reported studies in the west showed male predominance.<sup>14–17</sup> This difference in results may be due to the low number of patients in our series. However, no sex predilection was found in the COMS randomized prospective study.<sup>8</sup>

Local control rate of uveal melanoma treated by I-125 Radioactive plaque is more than 90%.<sup>17,18</sup> Similarly in this series, local control rate was 93%, and only 2 eyes were consequently enucleated after plaque therapy (one for painful neovascular glaucoma, and 1 for tumor progression 22 months after plaque therapy). Unfortunately even our ocular salvage rate was high, 38% of treated eyes had a visual acuity of less than 0.1 at last date of follow up. This finding might be explained by the delay in presentation after the onset of ocular complaints in the developing poor countries where health care could be unachievable because of the high cost or of far distance to travel. In our series 96% of tumors were of medium or large size at diagnosis.

Metastasis is common following a primary diagnosis of Uveal Melanoma (up to 50%); and in 90% of cases the liver is the target organ for metastasis.<sup>8,17</sup> In The COMS study, the estimated melanoma-related mortality was 1% at 5 years and was 4% at 8 years for patients with small melanomas.<sup>19</sup> The 5-year melanoma-related mortality increased to 10% for patients with medium-sized tumors, and increased to 28% for patients with large tumors.<sup>8,20</sup> While in our series, the metastasis rate was 14%, and the mortality rate was 11% even 96% of our patients had medium or large size melanoma. Our relatively lower rate of metastasis and death mostly due to the short follow up time (median follow up 24 months), and we expect to detect more metastatic cases during follow up for the same group of patients even those with tumor focal control. In the COMS, the liver was the predominant site of metastasis, which was reported in 89% of metastatic patients.<sup>21</sup> Our study showed metastasis in only 11% of patients and in all the liver was involved.

The visual outcome of treated eyes by radioactive plaque depends mainly on tumor size and locations, larger size are at greater risk of retinopathy (because of higher dose of radiation) and those located close to the optic disc are at risk of optic neuropathy, in addition to other factors such as retinal detachment, vitreous hemorrhage, and diabetes. Since most of our patients had large tumors that were mostly close to the optic disc and were associated with retinal detachment, they had worse visual outcome. Our small study size limited our ability to identify factors which may predict for local failure, melanoma related deaths, and poor visual outcome on statistical analysis.

In conclusion, our data and outcome support the use of Iodine-125 COMs plaque therapy at the inspection of implementation of plaque therapy in developing countries as it is easy for use mainly in dose calculation due to standard arrangement of seeds in the Silastic carrier and the simplicity of seeds insertion.<sup>9</sup> It can lead to eye salvage in more than 90% of cases, and reserves functional vision in more than 50% of cases. Our preliminary results are encouraging and are comparable to another countries worldwide. Even our results are not adding new science, they can be used as a model to successfully initiate radioactive plaque therapy as eye salvage program for uveal melanoma in underserved countries. Even uveal melanomas is rare in the middle east, awareness must be increased to enhance early detection that will lead to more salvage of eyes that harbor uveal melanoma and may enhance survival of affected patients.

This study was retrospective and of limited number and short follow-up after treatment. It is recommended to perform larger, multicenter and longer term follow-up studies with more insist on accurate and detailed gathering of information from patients before and after treatment in addition to comprehensive clinical and investigational exams in order to determine the true incidence, the predisposing risk factors, and the real outcome of management of uveal melanoma in our region.

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## Financial Disclosures & Conflict of Interest

None.

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