

Ru¹⁰⁶ Brachytherapy for Management of Choroidal Melanoma: Do we Need to Adjust Total dose According to the New NIST Calibration Measurement?

MOHAMED M. LOTAYEF, M.D.¹; IHAB S. OTHMAN, M.D.², F.R.C.S. (Glasg);
ABDALLAH E. SHELIL, M.D.³ and HATTEM KERIMA, F.R.C.S.⁴

The Departments of Radiotherapy, National Cancer Institute, Cairo University¹; Ophthalmology, Faculty of Medicine, Cairo University²; Ophthalmology, Faculty of Medicine, El-Azhar University³ and National Eye Centre Rod-EL Farag, Cairo⁴.

ABSTRACT

Purpose: To detect the need of adjusting the apical total dose according to the new NIST calibration measurement introduced by BEBIG Isotopen und Medizintechnik GmbH for the treatment of choroidal melanoma. As the total radiation dose should not be individualized depending on errors of previous calibration but can be applicable if based on a radiosensitivity test that was able to predict the final response of tumor to radiation for each particular patient.

Patients and Methods: Twenty patients with choroidal melanomas were treated between November 2002 and July 2004 at "Suzanne Mubarak Eye Tumor Centre", National Eye centre Rod-EL Farag, Cairo, Egypt. The prescribed dose was calculated according to the new NIST-calibrated dosimetry introduced by BEBIG, but without dose modification by using a conversion factor $F(\text{type},z)$ from the ASMW calibrated measurement to the NIST calibrated measurement that have been calculated depending on the plaque type and the distance z from the inner concave plaque surface along the central axis. For the treatment of choroidal melanoma in this study the apical dose ranged from 9000-10400cGy with a mean of 9855 ± 385 .

Results: After a follow up period from 12-28 months (median of 19 months) there was a local control rate of 100 % and the three years actuarial disease specific survival was 95% as only one patient died of liver metastases. Fourteen patients had a best corrected pre-treatment visual acuity of better than 6/60 in the affected eye. At the last follow up available, useful visual acuity of >0.5 was preserved in 7 of the patients.

Conclusion: Recalculation of the apical total dose (mostly increasing of the total dose) according to the conversion factor $F(\text{type},z)$, suggested by BEBIG after the new NIST calibration measurement, does not seem to have an effect on both local control and survival, in this study.

Key Words: Choroidal melanoma - Ru¹⁰⁶ - Plaque brachytherapy - NIST.

INTRODUCTION

There are multiple therapeutic options for treating choroidal melanomas. Enucleation was the only treatment option available for uveal melanoma for most of the last century [1]. However, in recent decades, with the emergence of more conservative treatment options that attempt to spare the affected eye and retain vision, the enucleation rate has substantially declined, but enucleation remains a common treatment for large tumors or in cases where there is no hope of regaining vision.

Brachytherapy is one such alternative treatment method now in widespread use for the treatment of choroidal melanomas. Brachytherapy using removable ophthalmic plaques are used as a primary treatment modality in intraocular tumors, whether benign or malignant, and as secondary treatment modality following failure of other conservative modalities [2].

Various materials for delivering brachytherapy have been investigated, beginning with radon in the 1930s. Lommatzsch pioneered the treatment of choroidal melanomas in 1964 using Ru¹⁰⁶ plaques, introducing these beta-emitting nuclides with directives for treatment [3].

Ruthenium-106 and iodine-125 is currently the most commonly used isotopes for plaque radiotherapy of choroidal melanomas, although cobalt-60, iridium-192, strontium-90, and palladium-103 have also been used. Modern techniques for plaque brachytherapy involve suturing a shielded plaque containing seeds of the

radioactive isotope to the sclera. The radiation dose is principally delivered to the base of the tumor, with a gradual lessening toward the apex. The plaque size is designed to include a margin of 2mm around the tumor. It is left in place until the calculated dose of radiation has been delivered, approximately five to seven days, then it is removed.

The Ru¹⁰⁶ ophthalmic plaques are concave shell-shaped structures consisting of a pure sheet of silver 1mm thick, which contains encapsulated material consists of Ru¹⁰⁶/Rh¹⁰⁶, a radioactive substance with a half life of 368.2 days and emits beta radiation with a maximum energy of 3.54 MeV and 20% gamma radiation with 0.512 MeV plus bremsstrahlung in the range from 0 to 3.54 MeV. The fused front window of the applicator on the concave side is 0.1mm and on the back is 0.9mm thick. It absorbs nearly 95% of the 3.54 mega-electron voltage (MeV) Beta radiation. The half life time is 368.2 days. The dose generated in tissue decreases after 7mm to one tenth of its value. This steep dose fall-off protects sensitive structures and renders best treatment results for tumors with a height up to 6mm. The surface dose rate is about 120 centigray (cGy) per minute, with an activity ranging from 10 to 50MBq (0.3-1.4 mCi), making it possible to apply a dose of 1000Gy at the base of the tumor and 100Gy at its apex in about 6 days. Ru¹⁰⁶ plaques are manufactured in 16 different sizes and shapes, by BEBIG Isotopen und Medizintechnik GmbH (Fig. 1).

Since its existence BEBIG has measured the energy dose rate according to the ASMW calibration (ASMW = standardization office of the former German Democratic Republic). This calibration uses special calibration factors for each type of plaque to compensate for the different geometry and the effects caused by the strong gradient. Most medical literature referring to the dosage of Ru¹⁰⁶ plaques refers to measurements with the ASMW calibration.

In 12 November 2002, BEBIG introduced the new NIST (National Institute of Standards and Technology USA) – calibrated dosimetry (http://www.bebig.de/downloads/augen_info_dosimetrie_engl.pdf). The depth-dose-curve in the new measurement protocol contains more (11) measurement points than the old one (4), giving more accuracy. Also the energy dose rate

distribution over the surface of the plaque is measured and displayed at more points. With introduction of the new NIST calibration the measurement uncertainty has improved and is now only $\pm 20\%$. NIST itself issues an uncertainty of $\pm 15\%$ to their calibration measurements.

When comparing the new NIST calibrated energy dose rates with the old ASMW calibrated results a difference is recognized that is for a number of plaque types within the old measurement uncertainty of $\pm 30\%$. For some plaques, however, the difference is larger than $\pm 30\%$ with increasing distance from the plaque.

It was suggested that the typical doses prescribed according to the ASMW calibrated measurements (ASMW-Gy) may not yield the same treatment results with the new NIST calibrated measurement results (NIST-Gy) and therefore needs adjustment.

For adjusting the total treatment radiation dose, BEBIG suggested a conversion factor $F(\text{type}_i, z_i)$ from the ASMW calibrated measurement to the NIST calibrated measurement that have been calculated depending on the plaque type and the distance z from the inner concave plaque surface along the central axis. The conversion factors were calculated by dividing the measurement results for the energy dose rate $DR(\text{type}_i, z_i)$ with 0.5mm detector and NIST calibration with the measurement results for the energy dose rate $DR(\text{type}_i, z_i)$ with 2mm detector and ASMW calibration:

$$F(\text{type}_i, z_i) = DR_{\text{NIST}}(\text{type}_i, z_i) / DR_{\text{ASMW}}(\text{type}_i, z_i)$$

where type_i is the plaque type and z_i the distance from the inner concave plaque surface along the central axis.

As an example a physician, who want to treat a choroidal melanoma with a CCB and typically prescribes a dose of 100Gy (ASMW) to the apex of the tumor. To reach the same treatment effect with the new NIST calibrated measurement, this physician needs to adjust the prescribed dose with the factor F according to Table (1) as follows:

Distance from CCB plaque	Conversion factor for CCB
0.0 mm	F= 0.87
2.0 mm	F= 1.01
3.5 mm	F= 1.11
5.0 mm	F= 1.21

For a tumor height of 2.5mm and a sclera thickness of 1mm he would prescribe a dose of 100Gy (ASMW) $\times 1.11 = 111\text{Gy}$ (NIST) to the apex, for a tumor height of 4mm a dose of 100Gy (ASMW) $\times 1.21 = 121\text{Gy}$ (NIST) to have the same treatment as with 100Gy (ASMW).

As the median apical dose prescribed by different authors ranged between 80-150Gy for ocular melanomas, with the dose prescribed with the old calibration standards, and because of the need to give a well defined fixed dose to the apex without change of this dose according to the size of the plaque, and as the total dose that is given to a particular type of tumor should not be individualized except if based on a radiosensitivity test that was able to predict the final response of tumor to radiation for each particular patient [4], we kept our dose in the range of 100Gy because until to date, no good radiosensitivity assay has been demonstrated.

MATERIAL AND METHODS

Twenty patients with choroidal melanomas were treated between November 2002 and July 2004 at "Suzanne Mubarak Eye Tumor Centre", National Eye centre Rod-EL Farag, Cairo, Egypt.

Our inclusion criteria were T1-3 choroidal melanoma tumors according to UICC TNM staging system, less than 6mm in height above the scleral surface. Exclusion criteria were tumors with evidence of extraocular extension (T4), diffuse intravitreal tumors or systemic metastases. All patients were followed up for at least 12 months after the application.

The prescribed dose was calculated according to the new NIST-calibrated dosimetry introduced by BEBIG, but without dose modification according to the plaque size.

In Table (2), it is shown the doses that we prescribed and the dose that would be given if we followed the BEBIG statement.

Five types of Ru¹⁰⁶ applicators (CCA, CCB, CCD, COB, and CGD) were used out of total of 16 different variations of type and size currently offered by the manufacturer (BEBIG GmbH Company). The plaque type is dependent on the indication for use, which is mainly the size and site of the tumor.

Investigations included tumor basal diameter and thickness evaluation measured by A/B-scan ultrasonography, orbital and brain computed tomography (CT) or magnetic resonance imaging (MRI) when indicated. Systemic patient evaluation was performed for evidence of metastases or other primary lesions. Systemic investigations included laboratory work, liver enzymes, abdominal ultrasound and chest X-ray.

A special plaque simulator computer program (distributed worldwide by BEBIG GmbH Company, under an exclusive license from the University of Southern California) was used to plot the exact tumor location using an eye model, with precise localization of the dimensions and distance to optic nerve, fovea, and lens. The appropriate Ru-106 plaque was selected, exteriorized on the sclera and centred on the tumor. Targeted apical dose, scleral dose, radiation decay, time of application, duration of dose delivery and time of removal of the plaque were calculated using the Plaque Simulator program. For the treatment of choroidal melanoma in this study the apical dose ranged from 9000-10400cGy with a mean of 9855 ± 385 .

Surgical Technique:

The surgical technique of radioactive plaque application involved performing a conjunctival periotomy and exposing the sclera in the area of the tumor. Transillumination or indirect ophthalmoscopy with scleral indentation was used to localize and mark the margins of the tumor on the sclera with a marking pen or diathermy. Optionally, the muscle was disinserted using the hang-back technique if the tumor extended beneath its insertion. A dummy plaque was placed on the sclera overlying the tumor base in all directions for at least 1mm and 5/0 monofilament non-absorbable nylon scleral sutures were placed through the superficial sclera in alignment with the holes in the arms of the plaque. The dummy plaque was removed, and the active plaque was grasped carefully with forceps. The serial number of the plaque was verified by the surgeon, and the radiation oncologist in the operating room. The plaque is placed on the sclera in correct alignment with the tumor by tying the pre-placed sutures through the holes in the arms of the plaque. The conjunctiva was then closed using 6-0 vicryl

sutures. Cycloplegic drops and steroid ointment were applied to the eye. An eye patch and a lead shield were applied to the eye.

The physicist from the department of radiation oncology performed a survey of radiation levels around the patient immediately following plaque application. Reversal of anaesthesia was induced and the patient was admitted with radiation precautions.

After the appropriate dose has been delivered, the plaque was removed under anaesthesia. The time of application ranged between 5 to 8 days depending on the activity of the plaque at time of the application, keeping the dose rate to the apex ≥ 60 Gy/hour.

Postoperative Follow-up:

The patient was discharged the same day of the plaque removal. The patients were instructed to apply cycloplegic drops and steroid ointment to the eye six times/day for three weeks. Follow up was scheduled in 1 month, and then every three months thereafter for the first year.

RESULTS

Of the 21 patients that were treated between February 2003 and July 2004, 20 were analyzable for this study. The patient who was excluded died because of unrelated accident 3 months after brachytherapy. The patients ranged in age from 45-62 (median 49). There were 6 females and 14 males. Twelve of the tumors were in the right eye and 8 were in the left. One patient suffered from diabetes and two had co-morbid

vascular disease (defined as a history of cerebrovascular, cardiovascular, or peripheral vascular disease but not hypertension alone). The follow up period ranged from 12-28 months (median of 19 months). Using the UICC TNM staging for ocular melanoma, 3 of the tumors were T1, 12 were T2, and 5 were T3. The anterior tumor margin was located anterior to the equator of the globe in 5 patients and posterior to the equator in 15 patients. Two tumors involved the ciliary body. Five tumors came to within 2mm or less of the macula and 3 came to within 2mm or less of the optic disc.

There was one death due to melanoma in the cohort, due to liver metastases. The three years actuarial disease specific survival was 95%. There were no patients alive with metastatic disease at the time of analysis (Table 2). There was no enucleation performed post treatment until the time of the analysis. Fig. (2) shows an example of tumor regression evident both by fundus examination and regression of tumor height by ultrasound.

Complications of plaque brachytherapy that did not require enucleation included radiation retinopathy in 9 patients, optic neuropathy in 3 patients, and glaucoma from rubeosis that was medically manageable in one patient. 18 of the 20 patients had adequate visual outcome data available for analysis. Fourteen of these patients had a best corrected pretreatment visual acuity of better than 6/60 in the affected eye. At the last follow up available, useful visual acuity of >0.5 was preserved in 7 of the patients.

Table (1): Conversion factor F(Type, z) depending on plaque type and distance z from the inner concave plaque surface along the central axis.

Type	Distance z			
	Surface (0 mm)	2 mm	3.5 mm	5 mm
CCA	1.11	1.39	1.54	1.54
CCB	0.87	1.01	1.11	1.21
CCC	0.75	0.85	0.90	0.92
CCD	0.90	1.00	1.14	1.31
CCX, CCY, CCZ	1.33	1.64	1.83	2.06
CGD	0.81	0.90	0.97	1.05
CIA	1.23	1.27	1.36	1.52
CIB, CIB-2	1.08	1.16	1.22	1.23
COB	0.94	1.03	1.17	1.27
COC	0.87	1.02	1.09	1.19
COE	1.07	1.29	1.48	1.57

The measurement uncertainty of these factors has been estimated to be $\pm 25\%$ (2s).

Table (2): The doses that we prescribed compared to the doses that would be given if we followed the BEBIG statement and its impact on survival.

Patient number	Tumor height	Ru ¹⁰⁶ plaque type	Radiation dose given in cGy	Recommended dose by BIBEG after conversion by F-factor	Follow up period in months	Follow up result after at least 12 months*
1	5.3	CCA	9000	13860	28	0
2	4.2	CCA	9500	14630	27	0
3	4.5	CCA	10000	15400	26	0
4	5.3	CCA	9600	14784	26	0
5	5.3	CCA	9800	15092	24	1
6	4.1	CCA	10200	15708	24	0
7	5.2	CCA	10000	15400	22	0
8	6.0	CCB	10400	12584	20	0
9	4.4	CCB	9600	11616	20	0
10	6.1	CCB	9900	11979	20	0
11	4.3	CCA	10400	16016	18	0
12	6.0	CCA	9700	14938	17	0
13	5.4	CCD	10100	13231	16	0
14	3.3	CCD	10200	11628	15	0
15	5	CCA	10100	15554	13	0
16	3	COB	9700	11349	13	0
17	4	CCA	9800	15092	13	0
18	3	CGD	9600	9312	12	0
19	4	CGD	9800	9751	12	0
20	4	CGD	10200	10149	12	0

*0: Surviving with no metastasis or local recurrence, 1: Died.

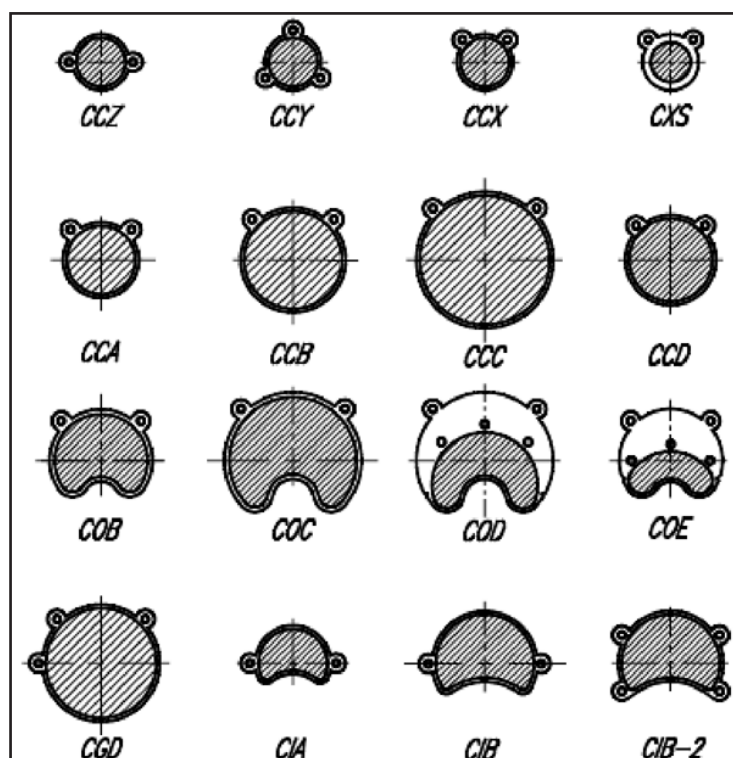


Fig. (1): For different applications there are 16 plaque types available.
 Uveal and choroidal melanomas: CCA, CCB, CCC, CCD and CGD.
 Retinoblastoma: CCX, CCY, CCZ and CXS.
 Ciliary body melanomas or melanomas close to the iris: CIA, CIB, CIB-2.
 Tumors close to the optical nerve: COB, COD, COE and COC.

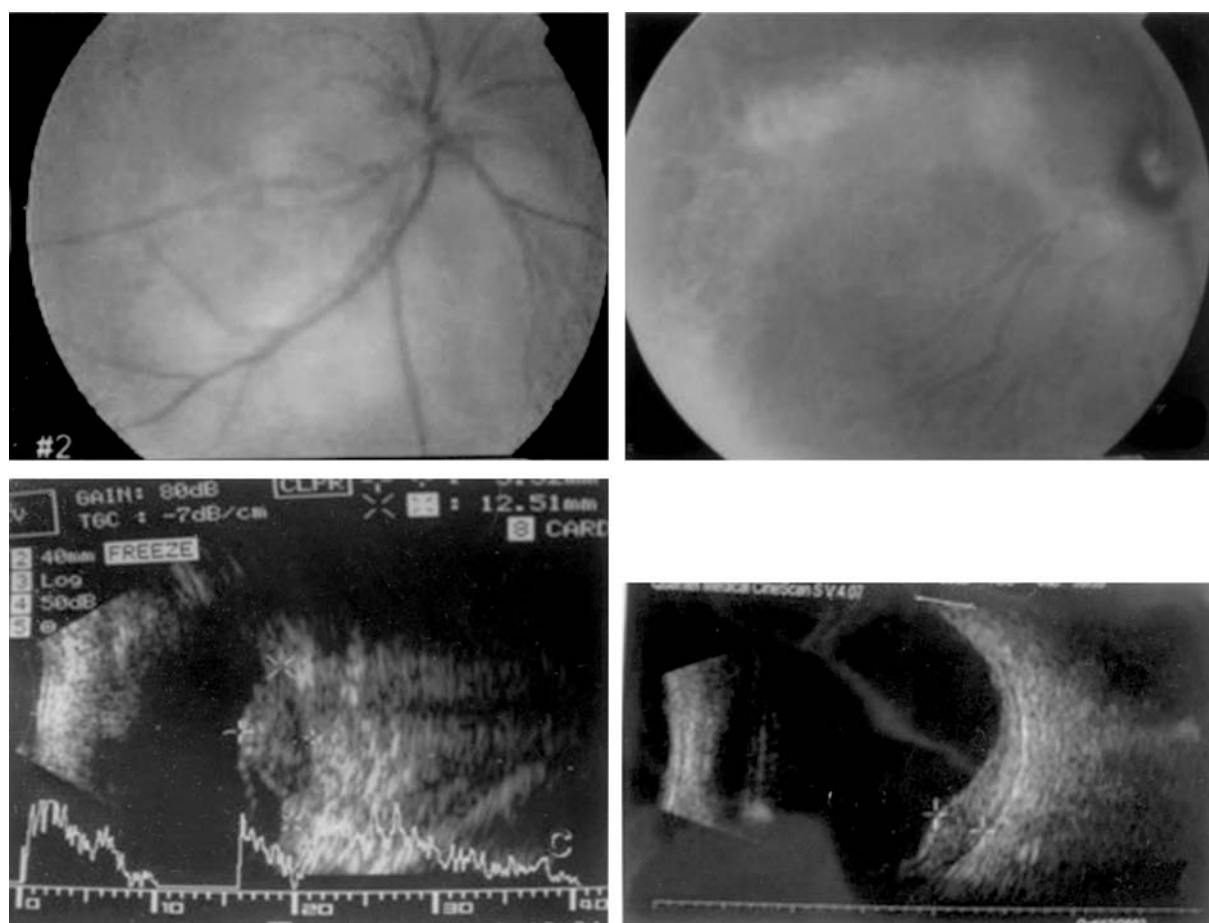


Fig. (2): A case with choroidal melanoma before (A & C) and 6 months after Ru¹⁰⁶ brachytherapy (B & D).

DISCUSSION

Seregard [5] undertook the first meta-analysis reviewing Ru¹⁰⁶ brachytherapy in which he pooled 5 case series from experienced European centres; He reported a disease specific 5-year survival of 86% for T1-T3 tumors with a median apical dose of 80-100 (ASMW-Gy).

Summanen et al. [6] and Lommatzsch et al. [7], gave a median apical dose of 100 (ASMW-Gy) and reported a disease specific 5-year survival of 78% and 89.6% respectively. In an effort to improve local disease control, Tjho-Heslinga et al. [8] increased the apical dose from 100 (ASMW-Gy) to 160 (ASMW-Gy) in 99 patients with small and medium-size uveal melanomas. They reported a 5-year disease-specific survival of 95% for the whole group. The best local control was achieved with an apical dose of >120Gy, and complications seemed to increase with a scleral dose of

>800Gy. However, these results should be viewed with caution as the follow-up for the “low-dose” group was significantly longer. Potter et al. [9] reported a 3-year disease-specific survival rate of 93% for patients treated with an apical dose of 150 (ASMW-Gy), while Kleineidam et al. [10], reported a disease specific 5-year survival of 84% when they gave a median apical dose of 250 (50-690) (ASMW-Gy), which was not superior to the rate with lower total doses.

Hermann et al. [11], studied the effect of dose escalation in their series with a median apical dose of 120 (83-322) (ASMW-Gy) and a result of 92% disease specific 5-year survival.

In our study the three years actuarial disease specific survival was 95% with a median dose of 100 (NIST-Gy), this is comparable with the above mentioned studies.

Useful visual acuity of >0.5 was preserved in 35% of the patients in our cohort. A final visual acuity >0.5 was found in 22.7% of the patients by Lommatzsch et al. [12], 27% by Potter et al. [9] and 42.4 by Tjho-Heslinga et al. [8].

The deterioration of vision was mainly influenced by the tumor location. Centrally growing melanomas have only a 30% chance of useful residual vision after therapy. The long-term follow-up by Lommatzsch [12] indicates that these results may even get worse because of scarring, retinopathy, and optic neuropathy.

Conclusion:

We believe our results compare favourably with previous reports in which doses were prescribed according to the ASMW calibrated measurements, despite the difficulty in comparing retrospective data from different centres because of variable follow-up times, tumor extension, and total doses used.

Ru^{106} brachytherapy optimal apical and scleral doses have not yet been found, however a total apical dose of 100Gy is accepted by most centres using this isotope. Recalculation of the apical total dose (mostly increasing of the total dose) according to the conversion factor $F(\text{type},z)$, suggested by BEBIG after the new NIST calibration measurement, does not seem to have an effect on both local control and survival. Though it is more accurate but in radiotherapy in general and brachytherapy in particular the total dose that is given to a particular type of tumor should not be individualized except if based on a radiosensitivity test that was able to predict the final response of tumor to radiation for each particular patient.

REFERENCES

- 1- The Collaborative Ocular Melanoma Study (COMS). randomized trial of pre-enucleation radiation of large choroidal melanoma I: Characteristics of patients enrolled and not enrolled. COMS report no. 9. *Am J Ophthalmol* 1998, 125 (6): 767-78.
- 2- Augsburger JJ, Gamel JW, Sardi VF, Greenberg RA, Shields JA, Brady LW. Enucleation vs cobalt plaque radiotherapy for malignant melanomas of the choroid and ciliary body. *Arch Ophthalmol*. 1986, 104 (5): 655-61.
- 3- Lommatzsch PK. Results after beta-irradiation ($^{106}Ru/^{106}Rh$) of choroidal melanomas: 20 years' experience. *Br J Ophthalmol*. 1986, 70 (11): 844-51.
- 4- Guirado D, Ruiz de Almodovar JM. Prediction of normal tissue response and individualization of doses in radiotherapy. *Phys Med Biol*. 2003, 48 (19): 3213-23.
- 5- Seregard S. Long-term survival after ruthenium plaque radiotherapy for uveal melanoma. A meta-analysis of studies including 1,066 patients. *Acta Ophthalmol Scand*. 1999, 77 (4): 414-17.
- 6- Summanen P, Immonen I, Kivela T, Tommila P, Heikkonen J, Tarkkanen A. Radiation related complications after ruthenium plaque radiotherapy of uveal melanoma. *Br J Ophthalmol*. 1996, 80 (8): 732-39.
- 7- Lommatzsch PK, Werschnik C, Schuster E. Long-term follow-up of $Ru-106/Rh-106$ brachytherapy for posterior uveal melanoma. *Graefes Arch Clin Exp Ophthalmol*. 2000, 238 (2): 129-37.
- 8- Tjho-Heslinga RE, Davelaar J, Kemme HM, de Vroome H, Oosterhuis JA, Bleeker JC, et al. Results of ruthenium irradiation of uveal melanomas: The Dutch experience. *Radiother Oncol*. 1999, 53 (2): 133-37.
- 9- Potter R, Janssen K, Prott FJ, Widder J, Haverkamp U, Busse H, et al. Ruthenium-106 eye plaque brachytherapy in the conservative treatment of uveal melanoma: Evaluation of 175 patients treated with 150Gy from 1981-1989. *Front Radiat Ther Oncol*. 1997, 30: 143-49.
- 10- Kleieidam M, Guthoff R, Bentzen SM. Rates of local control, metastasis, and overall survival in patients with posterior uveal melanomas treated with ruthenium-106 plaques. *Radiother Oncol*. 1993, 28 (2): 148-56.
- 11- Hermann RM, Pradier O, Lauritzen K, Ott M, Schmidberger H, Hess CF. Does escalation of the apical dose change treatment outcome in beta-radiation of posterior choroidal melanomas with ^{106}Ru plaques? *Int J Radiat Oncol Biol Phys*. 2002, 52 (5): 1360-66.
- 12- Lommatzsch PK, Alberti W, Lommatzsch R, Rohrwacher F. Radiation effects on the optic nerve observed after brachytherapy of choroidal melanomas with $^{106}Ru/^{106}Rh$ plaques. *Graefes Arch Clin Exp Ophthalmol*. 1994, 232 (8): 482-87.