Original Article

Short-term changes of cornea and tear film after ruthenium-106 plaque therapy for intraocular tumors

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Purpose: Plaque therapy is a well-recognized treatment for intraocular tumors. In current study, we aimed to prospectively investigate the short-term effects of ruthenium 106 (Ru-106) plaque therapy on the cornea and ocular surface parameters. **Methods:** Twenty-five patients diagnosed with choroidal melanoma which undergone Ru-106 plaque therapy from 2016 to 2018 were included. Tear osmolarity, tear film break-up time, Schirmer test I, fluorescein dye staining based on Oxford staining method; Ocular Surface Disease Index (OSDI) questionnaire and corneal specular microscopy were performed. These tests were assessed preoperatively and then 3 months postoperatively. **Results:** The mean (±SD) age of subjects was 48.52 ± 15.18 years. The patients were followed for a mean(±SD) period of 3.64 ± 2.40 months. Total mean (+SD) delivered radiation dose to the tumor apex and total received radiation by the sclera was 83.20 ± 26.31 and 640.65 ± 472.69 Gray (Gy), respectively. In longitudinal analysis, OSDI score and Oxford staining score increased significantly (P = 0.002 for both variables) and the prevalence of dry eye disease (DED) increased from 20% preoperatively to 72% at 3 months postoperatively (P = 0.001).The changes in the all specular microscopy parameters were statistically nonsignificant (all P values > 0.05). **Conclusion:** There is a considerable increase in the rate of DED following plaque therapy for the treatment of choroidal melanoma in short-term follow-up. The OSDI questionnaire and fluorescein staining test are valuable tools for early detection of DED postoperatively.

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Plaque therapy is a well-recognized treatment for uveal malignant melanoma and has been used in other intraocular tumors like choroidal hemangioma, retinoblastoma, capillary hemangioblastoma, and vasoproliferative tumors of retina.[1-5] Currently, ruthenium-106 (Ru-106) and Iodine-125 (I-125) are the most common radioisotopes used for plaque therapy. In spite of favorable outcomes of plaque therapy for intraocular tumors, they may have different side effects on adjacent normal intraocular tissues.[5,6] The major adverse effects are usually radiation related and manifest mostly in the posterior segment of the eye.[7] However, ocular surface's complications of plaque therapy including dry eye are usually overlooked.[8]

Different mechanisms have been reported for developing dry eye disease (DED) following plaque therapy including proximity of the plaque to lacrimal gland, damage to corneal and conjunctival epithelial cells, destruction of goblet cells on ocular surface, and iatrogenic ocular surface comprise during the surgery.[9,10]

DED is evaluated by well-known tests including tear film break-up time (TBUT) analysis, Schirmer test, tear osmolarity, Oxford staining score, and Ocular Surface Disease Index (OSDI) questionnaire.[11] Although, there is not a universal consensus on the evaluation of DED in clinical practice, it is recommended to use a combination of subjective and objective measures if available. Previous studies have evaluated the incidence of dry eye symptoms following plaque therapy for intraocular tumors and low rates (8–20%) have been reported for occurrence of DED.[7,9] However, these studies are usually restricted by relying on the subjective findings only for detection of dry eye.

In current study, we aimed to prospectively investigate the occurrence of DED following plaque therapy for treatment of choroidal melanoma using a combination of different objective methods for ocular surface evaluation.

Methods

This was a prospective interventional case series which conducted at Rassoul Akram and Noor eye hospitals between 2016 and 2018. The study was approved by the Eye Research Center Ethics Committee of the Iran University of Medical Sciences (IR.IUMS.FMD.REC 1396.931125700) and adhered to the tenets of the Declaration of Helsinki. Informed written consent was obtained. Patients with choroidal melanoma candidate for Ru-106 plaque therapy were enrolled in this study. Exclusion criteria were history of previous anterior segment surgery on the involved eye, history of previous

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herpes virus inoculation of the anterior segment, recent cataract surgery (less than 6 months), history of trauma or surgery on the nasolacrimal system, metastasis to the systemic organs due to ocular tumor, any significant pathology on the corneal endothelial examination by specular microscopy, any use of medications which may cause DED as a side effect, neurotrophic keratopathy, and moderate to severe DED secondary to autoimmune diseases at preoperative assessments.

Clinical and paraclinical assessments

All subjects underwent a comprehensive ocular examination preoperatively. Fundus photography, fluorescein angiography, and ocular ultrasound examination were carried out appropriately. The size and type of Ru-106 plaque was selected based on the tumor location, basal tumor diameter, fundus examination, and ocular ultrasonography findings, considering 2 mm safety margins. Tumor data including anatomical location, meridional location, anterior and posterior tumor margins, largest basal dimension (based on ophthalmoscopy), and maximum thickness (based on ultrasonography and ophthalmoscopy) were recorded. Radiation data including plaque type and size (CIA, CCA, CCB, COB, CGD), implantation time, radiation dose (Gray), and dose rate (Gray per hour) to the tumor apex and tumor base (0.6 mm from the surface of the plaque) were calculated.

Dry eye symptoms were collected using the validated Farsi version of the OSDI questionnaire.[12] Afterward, eyes were evaluated by specular microscopy (EM-3000, Tomey, Nagoya, Japan) for at least three consecutive evaluations by an experienced examiner and the most reliable results were documented. The selected image should have had at least 35 cells to be eligible for endothelial evaluation with clearly visible cell borders. Cell density, cell count, coefficient of variation of cell area, and hexagonality from the corneal center were calculated and recorded for every patient pre- and postoperatively.

The sequence of examinations was tear osmolarity (Tear lab, San Diego, CA), TBUT, fluorescein dye staining based on Oxford staining method, and Schirmer test I (without anesthetic use). To perform specific dry eye tests, the patients were educated to not using any topical eye drops 2 h prior to examination. For TBUT measurement, after using fluorescein dye and several blinking for uniform distribution of fluorescein film, the patients were instructed to refrain from blinking; then the minimum time between the last blink and the appearance of dry spot was measured in seconds. TBUT was performed in three consecutive times, and the mean time was recorded for each patient. Schirmer test I was done with rolled No. 35 Whatman filter paper inserted to the boundary of one-third lateral and two-third medial of the lower eyelid in the involved eye. The paper was held there for 5 min with closed eyelids.

According to the whole findings of these preoperative assessments and based on the latest TFOS DEWS II definition,[11] the diagnosis of DED was considered as follows: OSDI score of more than 13 (symptomatic patient) and one of the following sings: Schirmer test I score equal to or below 10 mm after 5 min with eyes closed, TBUT equal to or less than 10 s, Oxford staining score equal to or more than 3, or tear osmolarity equal to or more than 308 mOsm/L.[13]

Surgical technique

Ru-106 radioactive plaque (Bebig, Berlin, Germany, GmbH) was used for all patients. All procedures were performed under general anesthesia by senior surgeon (M.N.). Bulbar conjunctiva was dissected at nearest site to the tumor and the sclera was exposed. The exact location of the tumor was determined by scleral transillumination and/or indirect ophthalmoscopy. The plaque size was chosen based on the tumor diameter and 2 mm of safe margin. Based on the preoperative measurements, specific and calculated dose of the radiation was delivered to the tumor. The target radiation dose for tumor apex was 100 Gray (Gy) for choroidal melanoma, provided that the scleral doses did not exceed 1500 Gy.[14] Extraocular muscles were temporarily disinserted if needed. Temporary acrylic dummies were sutured to the sclera with 5-0 Mersilene on the tumor location. Then, radioactive plaque was sutured to the sclera at the preferred site and was kept there until the end of the calculated radiation time. Conjunctiva was repaired using 7/0 vicryl suture.[15-17] The treatment time was calculated based on the target radiation dose for the tumor, apex, and radiation dose rate. The plaque was removed in the operating room and conjunctiva was repaired at the end of the calculated radiation period.

Postoperative evaluation

Patients were scheduled for visit at the clinic 1 week, 1, 3, and 6 months postoperatively. Complete ocular examinations were done at each visit, but assessments of the ocular surface and tear film evaluation were carried out at 3-month visit.

Statistical analysis

Statistical analysis was performed using SPSS software (IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.). Shapiro-Wilk test was used to assess for normality of the data. Then, assessment of the changes in the anterior segment of the eyes was evaluated using Wilcoxon signed rank test. For assessing the effect of baseline characteristics on the changes of measured parameters, generalized linear mixed model was performed. *P* values less than 0.05 were defined as statistically significant.

Results

Twenty-five eyes of 25 patients were enrolled on this study. The mean and standard deviation (mean ± SD) of the apex dose and base dose were 83.20 ± 26.31 and 640.65 ± 472.69 Gy, respectively. The mean ± SD of radiation hours was 101.72 ± 71.65. Demographic features of the all subjects and tumor characteristics are summarized in Table 1.

The patients were followed for a mean period of 3.64 ± 2.40 months. From those measured parameters of DED, there were only significant alterations in the fluorescein staining score and OSDI results (*P* value = 0.002 for both variables) [Table 2]. On the other hand, based on the TFOS DEWS II definition, the prevalence of DED in preoperative assessment was 20% (5 eyes out of 25 eyes). However, 3 months after surgery, 13 new patients developed dry eye according to the same definition and the prevalence of DED increased to 72% (18 eyes out of 25 eyes) (*P* value = 0.001).

In generalized linear mixed model analysis, there was no association between changes in the fluorescein staining and OSDI scores and also baseline characteristics including gender, age, tumor dimensions, and radiation features (all *P* values > 0.05). In addition, the changes in the specular microscopy parameters were not statistically significant (all *P* values > 0.05) [Table 3].

Discussion

To the best of our knowledge, this is the first study that considers a combination of tear film assessments after Ru-106 plaque therapy for uveal melanomas. Our results revealed that patients may show considerable signs of DED after

plaque therapy with a significant increase in their OSDI score and oxford staining in short-term follow-up. These changes were found to be irrespective of the baseline characteristics of the patients including age, sex, tumor dimensions, and also importantly radiation features. There were also no significant alterations in the specular microscopy characteristics of the patients.

The tear film plays an important role in the function of ocular surface; including optical translucency, protection against microbial and infectious agents, and rapid healing of the superficial corneal ulcers.[18] Any ocular surgery including plaque therapy may affect the ocular surface, compromising tear film, and therefore result in exacerbation of the DED.[10]

Ru-106 plaque therapy is a very effective technique for intraocular tumors' control. Ru-106 emits a spectrum of β-particles that imposes lower radiation to the healthy and noninvolved eye structures such as the optic nerve, macula, and the lens in comparison to gamma-radiation of the I-125 plaques. However, it could be associated with posterior segment radiation side effects.[5,7] The complications related to plaque therapy are not only related to the tumor size and location, but also are correlated with the radiation dose and surgical technique. Usually, larger tumor size needs to be treated with a higher dose of radiation and subsequent radiation-related side effects such as cataract, retinopathy, and optic neuropathy may ensue.[7] There are only few retrospective studies, reviewing the effect of plaque therapy on the occurrence and progression of DED.[7,9,10,19]

Table 1: Baseline features and tumor characteristics of 25 patients

Gender (male %)	12 (48%)
Eye (OD %)	11 (44%)
Age (year)	48.52±15.18
Tumor dimensions (mm)	
Base 1	11.34±3.64
Base 2	9.41±5.67
Thickness	5.67±2.61
Radiation features	
Apex dose (Gy)	83.20±26.31
Base dose (Gy)	640.65±472.69
Apex dose rate (cGy/h)	1.29±0.67
Base dose rate (cGy/h)	6.07±1.34
Radiation hours	101.72±71.65

All values are shown as mean±SD, Gy=Gray

Table 2: Ocular surface measures of dry eye disease for 25 patients

Parameter	Preoperative#	Postoperative#	*P**
Schirmer (mm)	6 (4-10)	7.50 (5-8)	0.981
TBUT (seconds)	8 (5.50-11)	8 (4.50-8.50)	0.226
Oxford staining score	0 (0-3)	3 (0-4.50)	0.002
Tear osmolarity (mOsm/L)	318 (309-327)	317 (302-332)	0.419
OSDI score	2.25 (0-25)	25 (25-25.75)	0.002

#All values are shown as median with interquartile range. *Based on Wilcoxon signed rank test.

Patients may have DED before initiation of plaque therapy, which was found in 20% of our subjects in their preoperative assessment based on TFOS DEWS II definition.[11] In our study, OSDI and Oxford staining scores were worsened following plaque therapy, which is an expected finding, due to conjunctival and corneal epitheliopathy after plaque insertion and then removal. In a similar study, Shields *et al*.[20] studied 38 patients undergoing plaque therapy for melanoma of the iris and found corneal epitheliopathy in 9% of patients. In our study, Schirmer test I did not show any statistically significant change during the follow-up period. These findings may raise some important questions regarding the value of Schirmer test in earlier detection of DED following plaque therapy.

Heimann *et al*.[10] evaluated the histopathologic changes of the conjunctiva after plaque therapy for eyes with uveal melanoma. They found stromal fibrosis in the conjunctiva leading to goblet cell destruction and such findings were more prominent in plaque therapy comparing to pars plana vitrectomy. The decrease in goblet cell numbers and secondary changes of conjunctival epithelium in addition to alteration of lacrimal glands are the main factors contributing to the development of DED after radiotherapy.[9,10]

Quivey *et al*.[21] studied the effect of plaque therapy with I-125 in choroidal tumors and found that 8.3% of the patients developed DED in a meantime of 20 months after the procedure. They mentioned that the plaque therapy side effects are not only related to the tumor size and location, but also plaque type and surgical technique are other important factors. In current study, there was a high rate of DED (20%) before surgery, which increased to 72%at the 3-month visit after surgery. This high discrepancy between two studies might be justified by lack of the specific method for detection of DED in Quivey e*t al*.'s[21] study and using Ru-106 plaques in our investigation which emits radiation on both inner and outer surface in contrast to I-125 plaques in their study. In 2010, Razzaq *et al*.[22] in a long-term study reported the incidence of DED assessed by Schirmer, TBUT test, and Oxford staining following Ru-106 plaque therapy for irido-ciliary melanoma. They observed that dry eye syndrome developed in only 8.7% of patients, after 5 years. This lower rate of DED may be explained by thinner tumors with lower dose of radiation to ocular surface, less manipulation of conjunctiva during insertion of plaque in their report comparing to the posteriorly located and thicker tumors in our study. Alternative methods of radiotherapy for choroidal melanoma are also associated with dry eye. Gamma-knife radiosurgery with its detrimental effects on

Table 3: Specular microscopy measures of cornea for 25 patients

Parameter	Preoperative#	Postoperative#	*P**
Endothelial cell density (cells/mm^2)	2507.87±235.45	2512.91±249.18	0.434
Mean cell area (μm)	402.00±37.33	401.70±40.01	0.454
Hexagonality (%)	45.83±6.49	44.74±7.14	0.172
Coefficient of variation (%)	37.87±4.20	38.09±4.36	0.584
Central corneal thickness (μm)	524.27±43.47	519.25±45.82	0.588

#All values are shown as mean±standard deviation. *Based on Wilcoxon signed rank test.

the ocular surface and lacrimal glands also causes symptoms of dry eye in addition to reducing Schirmer test results and increasing staining scores.[23]

Lumbroso *et al*.[17] also studied 136 patients who have undergone plaque therapy with I-125 for choroidal melanoma and found keratitis in 0.08 and 2.8% of their patients 2 and 5 years after the procedure, respectively. However, it seems that dry eye symptoms and signs develop more rapidly than other major complications of the plaque therapy. The development of DED is related to surgical manipulation of the ocular surface in short-time period after the surgery, and lack of significant association between baseline radiation features and changes in tear film measures supports this hypothesis.

While there has been much research on plaque therapy, there are only few reports, which discuss the corneal endothelial cell changes in patients who have undergone plaque therapy for intraocular tumors. In our study, the specular microscopy findings after the surgery did not show significant differences in comparison to their preoperative values. In a similar study, Razzaq *et al*.[8] studied 33 patients with melanoma iridis who underwent Ru-106 plaque therapy and found a significant decrease in the corneal endothelial cell counts of the patients who had received phacoemulsification after plaque therapy, while the count was not decreased in the group who did not have cataract surgery.

Our study had its own limitations including low sample size, missed visits, and relatively short period of follow-up. Also, we confirm that our knowledge of the incidence of DED after Ru-106 plaque therapy is only limited to 3 months post plaque therapy and this could be a transient effect with no long-term complications. We suggest longitudinal studies with longer duration of follow-up to be performed in future, to see what would happen with these set of patients after plaque therapy, regarding dry eye.

Conclusion

In conclusion, our study showed that there is a high rate of DED following plaque therapy for uveal melanoma in short-term follow–up, and it is best evaluated by OSDI questionnaire and fluorescein staining test. Therefore, we recommend to evaluate all patients undergoing plaque therapy, pre- and postoperatively for early signs and symptoms of dry eye in order to promptly address the dry eye-related discomforts following plaque therapy. It would be prudent to recommend the patients to use artificial tears in the first 3 months after Ru-106 plaque therapy.

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Conflicts of interest

There are no conflicts of interest.

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