Review paper

Efficacy and complications of ruthenium-106 brachytherapy for uveal melanoma: a systematic review and meta-analysis

Saeed Karimi, MD[1,2], Amir Arabi, MD[1,2], Zahra Siavashpour, PhD[3], Toktam Shahraki, MD[1,2], Iman Ansari, MD[1,2]

[1]Ophthalmic Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran, [2]Department of Ophthalmology, Torfeh Medical Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran, [3]Department of Radiotherapy Oncology, Shohada-e Tajrish Medical Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran

Abstract

Purpose: The aim of this study was to evaluate the efficacy and vision-threatening complications of brachytherapy with ruthenium-106 (^{106}Ru) plaque to treat uveal melanoma.

Material and methods: A literature review was performed based on results from searching PubMed, Embase, Web of Science, Scopus, and Cochrane databases, using the following key words: "choroidal melanoma", "uveal melanoma", "brachytherapy", and "ruthenium-106". We included studies performed on more than 30 patients since 1986, reporting on local control rate, complications rate, mean radiation dose, and mean tumor thickness. The cumulative analysis was performed using Metaprop command of Stata v.16, and meta-regression was conducted based on mean tumor thickness and mean radiation dose to tumor's apex.

Results: Twenty-one retrospective studies were selected, involving 3,913 patients treated primarily with ^{106}Ru plaque brachytherapy. The range of radiation dose to tumor apex was from 70 Gy to 250 Gy. The local control rate following brachytherapy ranged from 59% to 98%, and the overall weighted mean of local control was 84%. However, the heterogeneity between studies' reports was remarkable (I^2 = 95.40%). Meta-regression based on tumor thickness and mean dose of radiation to the apex showed that the studies' heterogeneity was minimally related to the difference in mean tumor size (I^2 = 92%). The correlation between larger tumor size and lower local control rate was statistically significant (p-value = 0.024). There was no significant correlation between the mean radiation dose and local control rate (p-value = 0.679). The most commonly reported complications were cataract and radiation-related retinopathy.

Conclusions: Although the studies' heterogeneity was high, in a prescription dose ranging from 70 Gy to 250 Gy to the tumor apex, ^{106}Ru brachytherapy seems to be successful in local control of uveal melanoma. The efficacy of ^{106}Ru in controlling uveal melanomas decreased with the increase in tumor thickness. However, these outcomes should be verified in randomized comparative studies.

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Key words: uveal melanoma, choroidal melanoma, brachytherapy, complications, ruthenium-106.

Purpose

Treatment of uveal melanoma has been revolutionized since the development of eye-preserving plaque brachytherapy. Different radioactive isotopes have been used as a brachytherapy source for treating these tumors. In 1930, Moore used radon active seeds to treat a case of choroidal melanotic sarcoma. In his report, radon seeds of 1 millicurie strength were embedded in the tumor's thickest part [1]. Subsequent studies showed an evolution of ocular brachytherapy by introducing different radioisotopes and delivery devices. Nowadays, ocular brachytherapy plaques consist of gold, steel, silver, or titanium shells equipped with either low-energy photon emitter radioactive seeds or beta emitter isotopes. Iodine-125 (^{125}I), palladium-103 (^{103}Pd), and cesium-131 (^{131}Cs) as low-energy photon emitter radioactive seeds, and ruthenium-106 (^{106}Ru) as β emitter radioisotope, have been used as the radioactive plaque sources.

Using ^{106}Ru plaques for ocular melanoma began from primary studies performed by Lommatzsch *et al*. [2]. The half-life of ^{106}Ru can be six times as high as for ^{125}I [3]. Moreover, the simplicity to implant over the sclera, lower theoretical complication rate, and cost-benefit transportation to distant hospitals from manufacturer country (due to longer half-life) can be considered as the advantages of

Address for correspondence: Zahra Siavashpour, Department of Radiotherapy Oncology, Shohada-e Tajrish Medical Center, School of Medicine, Shahid Beheshti University of Medical Science, Tehran, Iran, phone: +98-912-029-8176, ✉ e-mail: z_siavashpour@sbmu.ac.ir, zahrasiavashpour@gmail.com

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using ^{106}Ru rather than the other isotopes. On the other hand, lower penetration power into the tumor has created controversies over the use of beta emitter ^{106}Ru in cases of large choroidal melanomas.

The present study aimed to meta-analyze the efficacy of ^{106}Ru brachytherapy to treat choroidal melanoma, review complications, and if applicable, to evaluate the relationship between tumor thickness and local control after brachytherapy with these kinds of plaques.

Material and methods

Our study consisted of 21 peer-reviewed retrospective case series on the efficacy of ^{106}Ru brachytherapy to treat uveal melanoma. PubMed, Embase, Web of Science, Scopus, and Cochrane databases were searched considering medical subject headings (MeSH) thesaurus for the literature published through July 31, 2020. Following key words were applied: "choroidal melanoma", "uveal melanoma", "brachytherapy", and "ruthenium-106" for the title, abstract, and keywords. Following the initial search, 872 papers were selected. Finally, extracted search results were exported to EndNote (Clarivate Analytics, version X7), as a known reference management software, and duplicated records were merged, resulting in 298 indexed papers. Studies presented as reports in meetings and conferences were not included in the review. We applied the following inclusion criteria to extract relevant articles: 1) available English language text, 2) performed on malignant uveal melanoma with or without involving anterior uveal tumors, 3) containing reports about mean or median radiation dose to the apex of the tumor, 4) information about mean or median follow-up time, 5) containing reports on the percentage of local recurrence, 6) including reports about the percentage of vision-threatening complications, such as cataract and glaucoma following brachytherapy, 7) using ^{106}Ru brachytherapy as a single primary treatment, 8) including more than 30 patients (eyes). Data were independently mined by three authors using a purpose-designed form. Following parameters were extracted from each study: number of patients, mean of tumor thickness (mm), follow-up time (months), radiation dose to tumor apex and sclera (Gy), local recurrence rate during follow-up (%), and rate of radiation-related cataract, glaucoma, papillopathy, and retinopathy (%). The present meta-analysis included the preferred reporting items for meta-analyses (PRISMA) checklist. Metaprop command Stata v.16 (StataCorp, Texas, USA) was used for data analysis. Estimates of the pooled proportion of local control and related confidence interval of 95% were combined using the inverse variance method. Between-study heterogeneity was assessed using Cochran Q and inconsistency index (I^2). It was considered statistically significant when p-value was lower than 0.05, or I^2 was higher than 50%. In case of a significant heterogeneity ($I^2 > 50\%$), a meta-regression analysis was used to evaluate the relationship between local control estimates and mean dose to the apex and mean tumor height.

Results

Twenty-one non-comparative observational studies were selected for this meta-analysis (Figure 1). Table 1 summarizes the studies included with their main de-

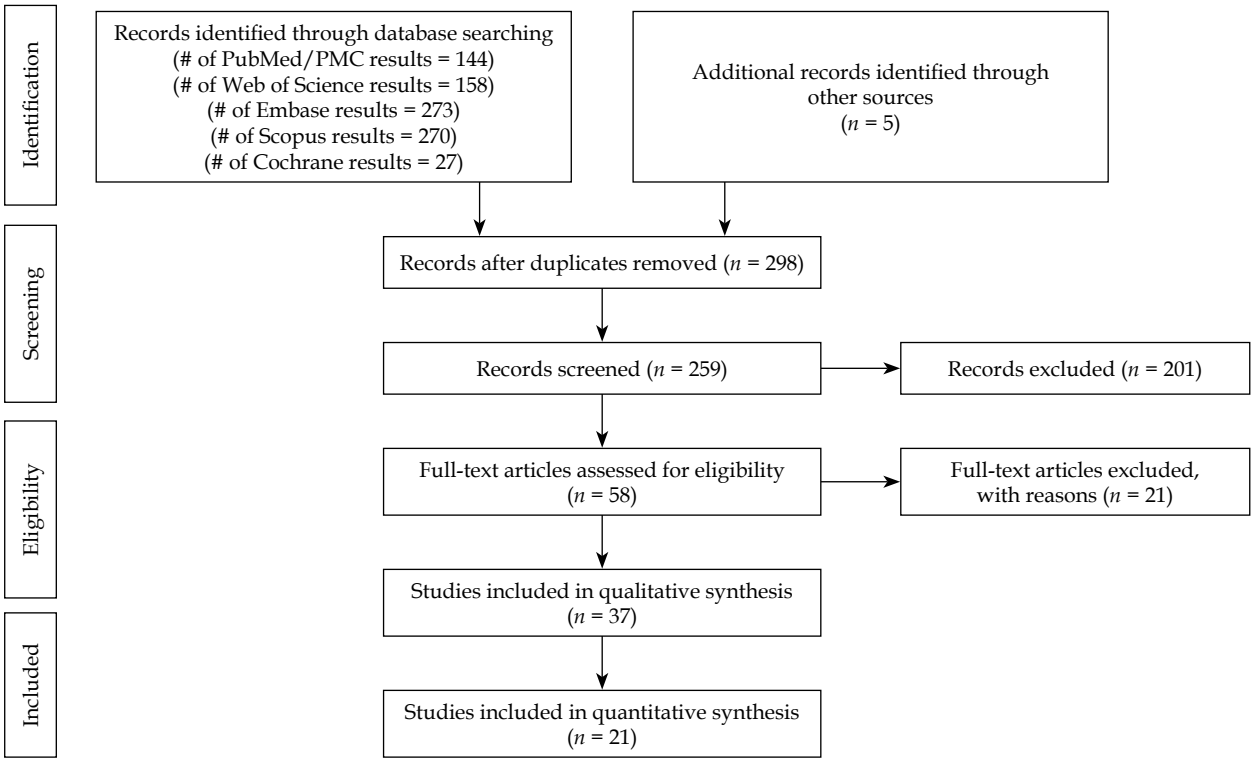

Fig. 1. Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flowchart summary

Table 1. Descriptive characteristics of included studies

Study [ref.]	Year	No. of patients	Mean tumor thickness (mm)	Mean dose to tumor apex (Gy)	Mean dose to sclera (Gy)	Mean follow-up (months)	Local control (%)	Post-treatment lens opacity (%)	Post-treatment glaucoma (%)	Retinopathy (%)	Papillopathy (%)
Jiang *et al.* [4]	2020	39	3.70	141.4	557.7	69.5	87.1	53.8	N.R.	28.2	10.3
Espensen *et al.* [5]	2019	226	3.90	100.0	N.R.	60.0	78.0	45.5	12.0	28.3	27.4
Rospond-Kubiak *et al.* [6]	2017	126	4.80	100.0	570.0	66.5	86.5	5.0	4.0	39.6	N.R.
Pagliara *et al.* [7]	2017	239	3.29	99.99	268.4	48.0	91.6	4.2	N.R.	25.5	5.4
Naseripour *et al.* [8]	2016	51	8.12	71.0	1269.0	36.1	82.4	37.2	N.R.	53.0	29.4
Fili *et al.* [9]	2015	952	–	100.0	–	37.9	72.0	N.R.	N.R.	N.R.	N.R.
Tarmann *et al.* [10]	2015	143	4.50	89.8	689.8	37.88	88.2	40.6	10.5	16.8	25.2
Salkola *et al.* [11]	2014	45	1.90	116.0	327.0	62.0	91.0	28.0	2.0	–	2.0
Takiar *et al.* [12]	2013	40	3.05	90.0	–	67.0	97.0	50.0	5.0	50.0	2.5
Perri *et al.* [13]	2012	133	3.26	100.0	800.0	92.4	82.7	15.0	0.0	24.0	2.2
Papageorgiou *et al.* [14]	2010	189	3.70	105.5	N.R.	33.0	85.7	N.R.	N.R.	N.R.	N.R.
Kaiserman *et al.* [15]	2009	63	9.29	69.9	N.R.	69.6	76.2	N.R.	8.0	N.R.	N.R.
Frenkel *et al.* [16]	2009	413	4.70	–	–	66.6	86.0	N.R.	N.R.	–	N.R.
Mossbok *et al.* [17]	2007	45	5.33	113.7	821.5	61.6	84.0	N.R.	N.R.	20.0	N.R.
Damato *et al.* [18]	2005	458	3.20	115.0	400.0	46.8	98.0	N.R.	N.R.	–	N.R.
Novak-Andrejcic *et al.* [19]	2003	65	4.79	100.0	N.R.	90.8	84.6	N.R.	N.R.	N.R.	N.R.
Georgopoulos *et al.* [20]	2003	41	5.00	137.0	977.0	55.0	98.0	N.R.	N.R.	N.R.	N.R.
Stoffelns *et al.* [21]	2002	52	3.20	105.0	N.R.	67.2	92.0	N.R.	2.0	40.0	20.0
Kleineidam *et al.* [22]	1993	184	3.50	250.0	747.0	73.2	82.0	N.R.	0.5	N.R.	N.R.
Summanen *et al.* [23]	1993	100	6.00	100.0	1000.0	33.6	59.0	2.6	10.0	N.R.	10.0
Lommatzsch *et al.* [24]	1986	309	N.R.	100.0	N.R.	80.4	69.9	N.R.	N.R.	N.R.	N.R.

N.R. – not reported

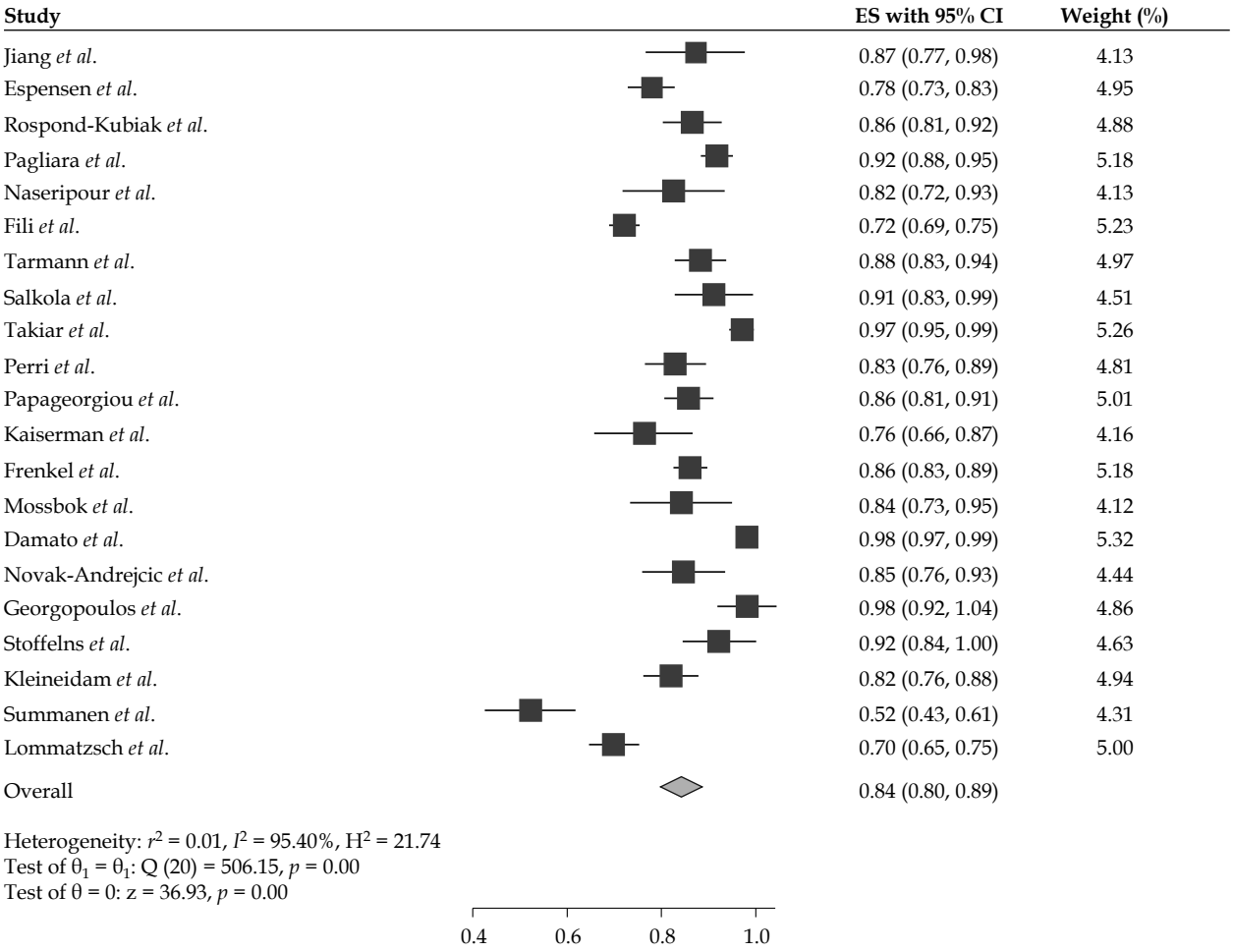

Fig. 2. Forest plot of 21 studies included in the meta-analysis to assess the efficacy of ^{106}Ru brachytherapy in the treatment of uveal melanoma

scriptive characteristics [4-24]. Collectively, the studies involved 3,913 uveal melanomas with ^{106}Ru brachytherapy plaques. The local control rate ranged from 59% to 98%, and the mean radiation dose to the apex of the tumor ranged from 70 Gy to 250 Gy.

A random-effect model was used to analyze the efficacy of the treatment. The treatment's overall efficacy in local control of the tumor was 84% (95% CI: 80-89%). The Cochrane Q analysis's p-value was less than 0.05, emphasizing the heterogeneity of the studies' results (Figure 2).

As the I^2 was 95.40%, the inconsistency between ^{106}Ru efficacy reports was concluded. To explore the reason, meta-regression analysis was performed based on the mean of tumor height and the radiation dose to apex. Following meta-regression, the I^2 index decreased to 92.52%, which showed that the inconsistency was not related to the heterogeneity between dose and tumor size (Figures 3, 4, and Table 2); however, the local control rate of the tumors was correlated with the mean tumor size (p-value = 0.024). More meta-regression and sub-group analysis were not applicable.

The analysis of ocular complications was limited by authors' poor reporting and was reflected in large and different results reported in the literature. According to the types of adverse effects, 14 studied described the rate of complications following brachytherapy [5, 6, 8-10, 14-16]. The rate of post-treatment retinopathy ranged from 20% to 53%. The rate of radiation-related crystalline lens opacity ranged from 4.2% to 53.8%. Radiation-related papillopathy and post-treatment ocular hypertension ranged from 2% to 29% and 2% to 12%, respectively.

Discussion

Our meta-analysis revealed a remarkable heterogeneity between the studies reporting the efficacy of ^{106}Ru brachytherapy to treat uveal melanoma. However, 19 out of 21 reviewed studies reported a local control rate of more than 70%, and the weighted mean of this rate reached 84%.

Although the results are not conclusive, recent comparative studies have changed the primary concepts regarding the inferiority of ^{106}Ru in local control of ocular melanoma. In a retrospective comparative case series with 2.5 years of follow-up, it has been reported that treatment with ^{106}Ru is as effective as ^{125}I [25]. Moreover, it has been suggested that ^{106}Ru brachytherapy may be superior to ^{125}I when the intended primary outcome is

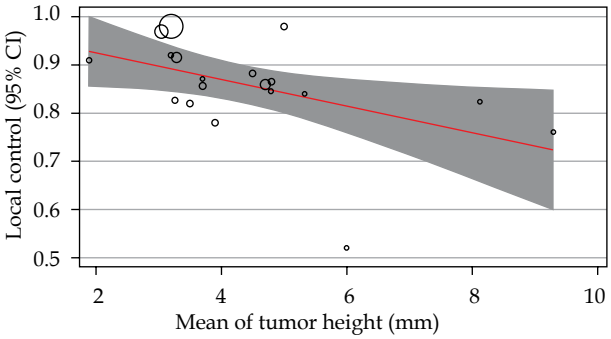

Fig. 3. The relationship between local control rates and mean tumor thickness. Circles were the surrogate for each study sample size

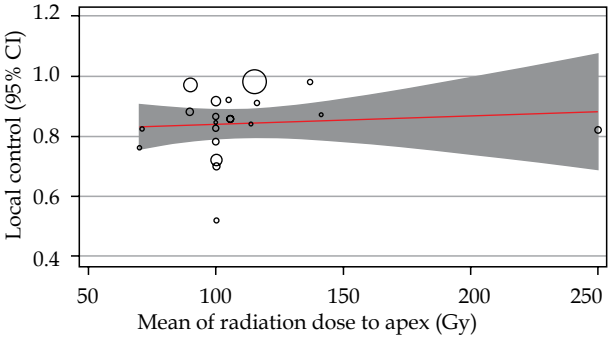

Fig. 4. The relationship between local control rates and mean radiation dose to the apex of the tumor. Circles were the surrogate for each study sample size

Table 2. The results of meta-regression based on tumor height and mean dose to the apex

Variable of meta-regression	Number of included studies	Coefficients	*P*-value	95% CI	Report of heterogeneity
Tumor height	19	–0.027	0.024	–0.0518/–0.003	Q = 154.34 *P*-value < 0.001 I^2 = 92.52
Radiation dose to the apex	20	0.0002	0.679	–0.0010/0.0016	Q = 497.04 *P*-value < 0.001 I^2 = 95.69

CI – confidence interval

a reduction of thickness of melanoma. In another study comparing long-term efficacy and safety profiles of ^{106}Ru and ^{125}I brachytherapy, it was reported that both methods resulted in favorable control of the tumor, but ^{106}Ru may provide additional benefit with reduced toxicity in tumors less than 5 mm of height [3].

The lower penetration power of ^{106}Ru has limited its usage for melanomas thicker than five mm [3, 26]. Lack of reports on the effectiveness of ^{106}Ru brachytherapy in treating large uveal melanoma makes it impossible to present a definite conclusion. In our study, 4 out of 21 reports have used ^{106}Ru brachytherapy for tumors with a mean thickness of more than 5 mm, and reported rates of local control ranged from 59% to 84%. However, based on the negative slope of meta-regression, the thickness of uveal melanoma may be a predicting factor for the success of ^{106}Ru brachytherapy, where the response of larger tumors could be lesser compared to smaller melanomas. Also, a minimal part of the heterogeneity in reported success rates was related to the tumors' mean size.

Based on the previous reports and our analysis results, tumor location and radiation dose to the tumor's apex seem to be additional determinants of therapeutic response to ^{106}Ru plaque brachytherapy. It was suggested that the tumor location may be as important as the size of the treatment's efficacy. In a study by Barker *et al.*, tumors close to the edge of optic disc or the center of fovea, in addition to the cases with posterior tumor border near the posterior pole, were significantly associated with a higher rate of local recurrence. It may reflect the importance of tumor bulk coverage by the radiating plaque since, in the same study, smaller plaque diameter relative to the tumor's largest base diameter was one of the predictors of ^{106}Ru plaque brachytherapy failure [27].

In our meta-analysis, the correlation between the local control rates and the apex's mean dose was positive but not statistically significant. Dose prescriptions for choroidal melanoma typically ranged from 70 Gy to 100 Gy to the tumor's apex, with a treatment duration of 3 to 7 days. Although it may be interpreted as the presence of similar efficacy for different doses of apex radiation within the range of 70 Gy to more than 100 Gy, further studies should be conducted to evaluate this concept reliably. It would be logical to use lower doses to diminish the treatment's short-term and long-term complications.

Predictably, the cumulative rate of local recurrence increases during the follow-up period. In a recent retrospective study, the local tumor recurrence rate increased from 3% at 12 months to nearly 15% at 48 months [10]. Similarly, uveal melanoma's survival rates could decrease from 81.6% at five years to around 60% at ten years [10, 28]. After plaque brachytherapy, patients included in this review were followed for local control and complications with an interval of 3 to 6 months, and a follow-up duration of 1 to more than six years. The most common vision-threatening complications of ^{106}Ru brachytherapy are retinopathy and cataract. However, ocular hypertension and optic neuropathy were also reported as complications of this treatment technique. According to the miscellaneous reports on the complications, plaque brachytherapy has also been associated with ocular surface disorders, sclera integrity, and ocular muscle functions [6, 10, 13, 22]. These complications must be treated through standard protocols to prevent loss of visual function and quality of life.

It seems that the preservation of visual acuity has been the primary goal of using beta-emitter isotopes in plaque brachytherapy. In preliminary non-comparative reports, assumed complications, such as neovascular glaucoma, are less common in patients treated with ^{106}Ru [2]. According to previous reports, main risk factors associated with lower final visual acuity were older age, posterior and temporal tumor location, larger tumor, and posterior extension of the lesion [29]. Conservation of a visual acuity better than 20/200 and finger-counting were expected at long-term follow-up in 55% to 60% and over 80% of eyes treated with ^{106}Ru, respectively [18]. Bergman *et al*. reported that up to 50% of patients treated with ^{106}Ru were expected to have a visual acuity better than 0.1 in five years after the treatment [30].

Conclusions

The present study involves a systematic review of 21 retrospective studies. Our review's main limitation was the retrospectivity of included studies, which made it impossible to perform a formal meta-analysis, since there were no randomized trials and prospective studies were rare. However, published studies suggest that plaque brachytherapy with ^{106}Ru is successful in local control of uveal melanoma. Cataract and retinopathy are the main vision-threatening complication of radiation. Although pooled data analysis reveals a higher success rate in smaller tumors, this effect should be verified in randomized comparative studies.

Disclosure

The authors report no conflict of interest.

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