Histopathology-guided management of ocular surface squamous neoplasia with corneal stromal or scleral invasion using ruthenium-106 plaque brachytherapy

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Received 2 March 2021
Accepted 7 November 2021

To cite: Rao R, Honavar SG, Lahane S, *et al*. *Br J Ophthalmol* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/bjophthalmol-2021-319201

ABSTRACT

Background/aim To evaluate the safety and efficacy of ruthenium-106 (Ru-106) plaque brachytherapy in managing invasive ocular surface squamous neoplasia (OSSN).

Methods This is a retrospective, non-comparative, interventional case series of 42 eyes with OSSN with histopathologically-proven corneal stromal and/or scleral invasion that underwent Ru-106 plaque brachytherapy. Main outcome measures were tumour regression, eye salvage, final visual acuity, treatment complications and metastasis.

Results At presentation, the mean tumour basal diameter was 9.3 mm (range 5–26 mm) and thickness 3.1 mm (range 1.5–11 mm). Prior treatment included excision biopsy in two patients (5%), incision biopsy and topical interferon in one each (2%). Following excision with 4 mm clinically clear margins, corneal stromal and/or scleral invasion of OSSN was confirmed in all 42 cases, with the excised base showing invasive squamous cell carcinoma. A total dose of 5000 cGy over a mean duration of 19.7 hours (range 7–41 hours) was provided to an axial depth of 2 mm using Ru-106 surface plaque. Over a mean follow-up of 36.9 months (range 22.3–72 months), complete tumour regression was achieved in all eyes (100%). Two eyes (5%) showed conjunctival tumour growth remote from the site of prior treatment. Visual acuity was maintained at ≥20/200 in 35 eyes (83%), with a loss of >2 Snellen lines in 1 eye (2%). There was no evidence of regional lymph node or systemic metastasis.

Conclusion Histopathology-guided use of Ru-106 surface plaque brachytherapy is a safe and an effective adjuvant therapy in the management of corneal stromal and/or scleral invasion of OSSN.

INTRODUCTION

Ocular surface squamous neoplasia (OSSN) is an umbrella term for premalignant and malignant epithelial tumours of the conjunctiva including dysplasia, carcinoma in situ and invasive squamous cell carcinoma.[1–5] While carcinoma in situ extends through the entire thickness of the conjunctival epithelium and does not invade beyond the basement membrane, invasive OSSN has gross or microscopic invasion into the adjacent tissues.[1 2 5] Invasive OSSN commonly extends to involve the corneal epithelium and rarely, corneal stroma.[1–5] The tumour can also extend into the sclera, anterior segment or the orbit in advanced cases.[1–5] Patients with HIV infection also frequently have aggressive and invasive tumours.[1–3 5]

Radiotherapy for the management of ocular surface tumours is gaining popularity in the past few decades, both as an adjuvant treatment and as a part of primary management.[6–20] Initially, X-rays were used with good tumour control, but plaque brachytherapy soon gained popularity.[6–20] Plaque brachytherapy helps in providing targeted treatment to the tumour base with limited exposure of the normal tissue to the effects of radiation. The earliest reports of the use of plaque brachytherapy in OSSN were using strontium-90, a source of beta radiation, which is known to be safe by providing precise, low-penetration radiation, thus limiting exposure to the deeper and surrounding normal tissue.[7–11] However, the production of strontium-90 in a readily usable form is limited and so is the availability in most parts of the world. This study evaluates the efficacy of an easily available and a common source of beta radiation, Ru-106, as an adjuvant treatment in the management of OSSN with histopathologically proven corneal stromal and/or scleral invasion.

METHODS

This is a retrospective, non-comparative, interventional consecutive case series of 42 eyes of 42 patients with OSSN with histopathologically proven corneal stromal and/or scleral invasion following excision biopsy. The primary objective was to assess tumour control with plaque brachytherapy. The study setting was an integrated ocular oncology centre at a tertiary care eye hospital.

The medical records of 42 patients who underwent plaque brachytherapy were retrospectively reviewed. Ocular features included the presenting complaint, laterality of OSSN, eye involved, best-corrected visual acuity (BCVA), tumour number, tumour location (limbal, bulbar), quadrant location (nasal, temporal, superior and inferior), maximum tumour basal diameter (in mm) and thickness (in mm), corneal involvement, scleral fixity and presence of any intraocular or orbital extension. The tumour basal diameter was measured with slit lamp biomicroscopy. Tumour thickness was estimated with slit lamp biomicroscopy, and anterior-segment optical coherence tomography (AS-OCT) or ultrasound biomicroscopy (UBM). Intraocular extension was excluded by using slit lamp biomicroscopy,

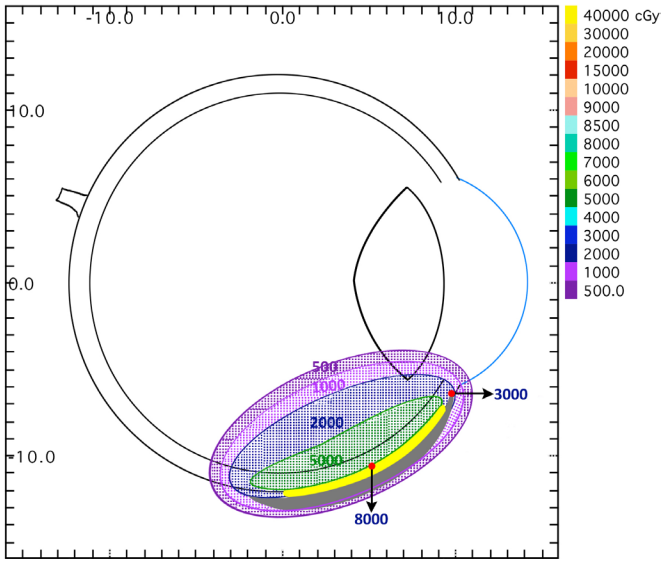

Figure 1 Simulated isodose curves showing radiation dose distribution at various depths at the centre and periphery on placement of the Ru-106 episcleral plaque with its anterior edge at the limbus using the BEBIG plaque simulator software PS5 (Eckert and Ziegler BEBIG, Berlin, Germany). The tumour is represented by the colour yellow and the plaque by the colour grey. The figure shows that the episclera, in this case, has received a dose of 8000 cGy in the centre, with 5000 cGy delivered as intended at 2 mm depth (green) to the entire extent of the tumour. The peripheral edge of the plaque is estimated to receive a dose of 3000 cGy at the level of the episclera. Ru-106, ruthenium-106.

gonioscopy, indented peripheral fundus examination, AS-OCT and/or UBM or 3-Tesla MRI. Patients with definite clinical or radiological evidence of intraocular extension were not included in the study. Photographic and diagrammatic documentation of the tumour pretreatment and post-treatment was performed to monitor any local recurrence of tumour.

The primary treatment protocol in all patients included excision of the tumour with 4 mm clinically clear margins and double freeze-thaw cryotherapy to the resected conjunctival edges. The corneal epithelial component was managed by alcohol-assisted keratoepitheliectomy, corneal stromal invasion by lamellar keratectomy, and the scleral invasion by superficial lamellar sclerectomy, followed by ocular surface reconstruction with preserved human amniotic membrane graft and fibrin glue. The biopsy specimen was carefully placed over Whatmann 42 filter paper, oriented accurately in its anatomical position with margins unrolled and marked, and submitted for histopathological examination. The pathologist was specifically requested to report on the tumour invasion of the excised corneal and scleral base, its location and extent. Patients with confirmed involvement of the corneal and/or scleral base with invasive OSSN on histopathology were treated secondarily by plaque radiotherapy after complete epithelisation of the ocular surface, between 4 and 6 weeks after the primary surgery. The time interval between the primary surgery and plaque brachytherapy was noted.

Dosimetry was performed by a radiation physicist with a dose of 5000 cGy to 2 mm depth. A ruthenium-106 (Ru-106) plaque (Eckert and Ziegler BEBIG, Berlin, Germany) was applied over the excised tumour base ensuring complete coverage of the tumour base with at least an additional 2 mm margin (figure 1). Ru-106 CCA (15.3 mm basal diameter) was used in tumours up to 11 mm basal diameter, type COB (19.8 mm basal diameter) was used in tumours up to 15.5 mm basal diameter and the plaque was rotated to cover the entire base in tumours larger than 15.5 mm in basal diameter). After the completion of treatment, the patients were monitored on day 1, week 1, week 6, then 3-monthly for 1 year, 6-monthly for 3 years and annually thereafter. The clinical data were tabulated and analysed with regard to the main outcome measures—tumour regression, eye salvage, final visual acuity, treatment complications and metastasis. Complete tumour regression was defined as no tumour recurrence in the area of radiation at least for a year of follow-up after the surgery. Tumour recurrence was defined as tumour growth in the same location as the previous tumour or at its margin. Remote tumour location was defined as tumour growth beyond the location of the previous tumour or its margin.

Table 1 Ru-106 plaque brachytherapy in OSSN with corneal stromal/scleral invasion: patient demographics

Demographics	n=42 patients (%)
Age	
Mean, years	49.5
Median (range), years	48 (26–83)
Race	
Asian Indians	42 (100)
Sex	
Male	28 (74)
Female	14 (26)
Presence of systemic disease	
Diabetes	4 (10)
HIV positivity	2 (5)
Hepatitis B	3 (7)
Xeroderma pigmentosum	0 (0)
Presenting complaint	
Painless mass	38 (90)
Redness	4 (10)

OSSN, ocular surface squamous neoplasia; Ru-106, ruthenium-106.

RESULTS

There were 42 eyes of 42 consecutive patients treated with Ru-106 plaque brachytherapy over an 8-year period. The demographics of the patients are listed in table 1.

The clinical features of the patients at the time of presentation have been elaborated in table 2. At the time of diagnosis, 38 eyes (90%) had visual acuity ≥20/200. All patients had unilateral involvement and presented with a single tumour. Majority were in limbal location (n=40, 95%) and in nasal/temporal bulbar conjunctiva (n=40, 95%). Papillomatous morphology was present in three eyes (7%), diffuse OSSN in two eyes (5%), while rest of them were nodular (n=37, 88%). The mean basal diameter of the tumour was 9.3 mm (median 8.7 mm; range 5–26 mm) and the mean tumour thickness 3.1 mm (median 4 mm; range 1.5–11 mm). While 39 eyes (93%) showed corneal extension of the tumour and 39 eyes (93%) had clinically apparent scleral fixity and scleral invasion on AS-OCT (16) or UBM (26), none of the eyes in the series had evidence of intraocular extension at the time of presentation. Intraocular extension was assessed using slit lamp biomicroscopy (n=42), gonioscopy (n=28), indented peripheral fundus examination (n=26), AS-OCT (n=16), UBM (26) or 3-Tesla magnetic resonance imaging (n=8). Prior treatment before referral included excision biopsy in 2 patients (5%), incision biopsy in 1 (2%) and topical interferon in 1 (2%).

Table 3 elaborates the treatment and outcomes. Every patient in the series underwent primary tumour excision and histopathological evaluation. On histopathology, one eye (2%)

Table 2 Ru-106 plaque brachytherapy in OSSN with corneal stromal/scleral invasion: clinical features

Clinical characteristics	n=42 eyes (%)
Tumour laterality	
Unilateral	42 (100)
Bilateral	0 (0)
Eye involved	
Right eye	22 (52)
Left eye	20 (48)
Visual acuity	
20/20–20/40	28 (67)
20/50–20/200	10 (24)
<20/200	4 (10)
Intraocular pressure, mm Hg	
Mean (median, range)	17 (16, 11–22)
No of tumours per eye	
Mean (median, range)	1 (1,1)
Tumour location	
Limbal	40 (95)
Bulbar	2 (5)
Quadrant location	
Nasal	19 (45)
Temporal	21 (50)
Inferior	1 (2)
Superior	1 (2)
Tumour morphology	
Nodular	37 (88)
Papillomatous	3 (7)
Diffuse	2 (5)
Tumour basal diameter, mm	
Mean (median, range)	9.3 (8.7, 5–26)
<11 mm	28 (67)
11.1 to 15.5 mm	13 (31)
>15.5 mm	1 (2)
Tumour thickness, mm	
Mean (median, range)	3.1 (4, 1.5–11)
Corneal involvement	
Yes	39 (93)
No	3 (7)
Scleral fixity	
Yes	39 (93)
No	3 (7)
Tumour extent	
Intraocular	0 (0)
Orbital	0 (0)

OSSN, ocular surface squamous neoplasia; Ru-106, ruthenium-106.

Table 3 Ru-106 plaque brachytherapy in OSSN with corneal stromal/scleral invasion: treatment and outco

Treatment and outcomes	n=42 eyes (%)
Previous treatment	
Topical interferon	1 (2)
Incision biopsy	1 (2)
Excision biopsy	2 (5)
Histopathology	
Excision margin positivity	1 (2)
Excision base positivity	42 (100)
Corneal stromal base only	1 (2)
Scleral base only	31 (74)
Both corneal stromal and scleral base	10 (24)
Time interval between excision and plaque radiotherapy, weeks	
Mean (median, range)	4 (4, 4–15)
Type of plaque used	
CCA*	29 (69)
COB	13 (31)
Total dose, cGy	
Mean (median, range)	5000 (5000, 5000)
Duration of treatment, hours	
Mean (median, range)	19.7 (18.9, 7–41)
Duration of follow-up, months	
Mean (median, range)	36.9 (30.4, 22.3–72)
Complications from plaque radiotherapy	
Recurrent corneal epithelial defect	2 (5)
Further management during follow-up, n=2	
Plaque brachytherapy treatment for tumour growth at remote site	2 (5)
Enucleation	0 (0)
Exenteration	0 (0)
Visual acuity at final follow-up	
20/20–20/40	27 (64)
20/50–20/200	8 (19)
<20/200	7 (17)

*CCA (15.3 mm) plaque was used in one patient with rotation to cover the entire tumour base.
OSSN, ocular surface squamous neoplasia; Ru-106, Ruthenium-106.

showed excision margin positivity with carcinoma-in-situ while all the 42 eyes (100%) had invasive OSSN involving the excision base (American Joint Committee on Cancer, Eighth Edition, T3/N0/M0). In all, 1 (2%) involved the corneal stroma alone, 31 (74%) involved the scleral base alone and 10 (24%) involved both. Adjuvant treatment with plaque brachytherapy was performed after a mean period of 4 weeks (median, 4 weeks; range 4–15 weeks) after the primary surgery. The type of Ru-106 plaque chosen depended on the largest basal diameter of the tumour—type CCA (15.3 mm basal diameter) was used 28 eyes (67%), type COB (19.8 mm basal diameter) in 13 eyes (31%) and the plaque was rotated to cover the entire base in 1 eye (2%). Brachytherapy included the cornea in 39 eyes and was limited to the sclera in 3 eyes. The extent of cornea included in brachytherapy ranged from 3 to 8 mm (median 5 mm). A dose of 5000 cGy was provided to 2 mm depth over a mean duration of 19.7 hours (median, 18.9 hours; range 7–41 hours).

Over a mean follow-up duration of 36.9 months (median, 30.4 months; range, 22.3–72 months), all (100%) patients showed complete tumour regression (figures 2–4). Two eyes (5%) manifested tumour growth at a mean follow-up of 4 months (median 4 months; range 3–5 months) at a site remote from the original tumour location. Both were successfully treated with excision biopsy. None of the patients had regional lymph node metastasis or systemic metastasis. All the 39 eyes where brachytherapy covered part of the cornea had an epithelial defect at the base that resolved in 3–7 days following brachytherapy on topical lubricants. Two patients (5%) had postradiotherapy recurrent corneal epithelial defects which resolved with topical lubricants and temporary suture tarsorrhapy (1) and bandage contact lens (1). BCVA at the final follow-up was ≥20/40 in 27 eyes (64%), 20/50 to 20/200 in 8 eyes (19%) and <20/200 in 7 eyes (17%). While 10 eyes (24%) had visual improvement >2 Snellen lines and 31 (74%) were stable, 1 patient (2%) had deterioration of vision >2 Snellen lines.

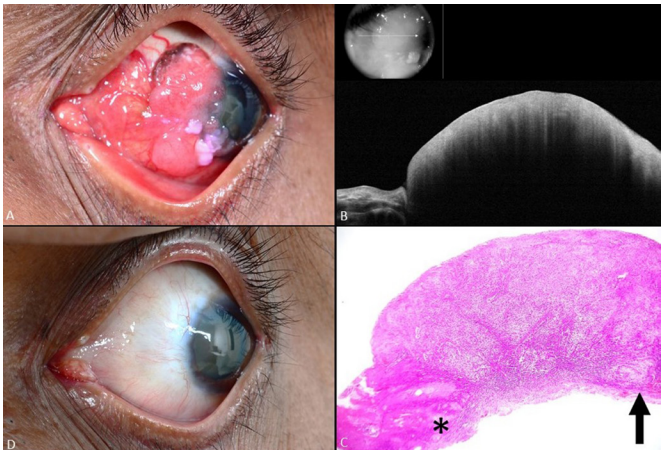

Figure 2 Left eye OSSN clinically involving the cornea and sclera, (A) AS-OCT showed posterior shadowing and the base could not be evaluated, (B) however, intraoperative findings were suggestive of corneal stromal and scleral invasion. Histopathology following excision biopsy confirmed the diagnosis of invasive squamous cell carcinoma with clear excision margins. The tumour, however, extended to the base both in the cornea (asterisk) and sclera (arrow) (H&E, OMX40), (C) 15 months after Ru-106 plaque brachytherapy, the patient has complete local tumour control, (D). AS-OCT, anterior-segment optical coherence tomography; OSSN, ocular surface squamous neoplasia; Ru-106, ruthenium-106.

DISCUSSION

OSSN is managed by topical chemotherapy (mitomycin-C and 5-flurouracil) and immunotherapy (topical or injection interferon alpha-2b),[21–24] or by complete excision with wide clear margins.[25] For tumours with corneal stromal invasion, a lamellar keratectomy is performed, while for those with scleral involvement, a lamellar sclerectomy is additionally performed.[25] However, for deeper scleral invasion, deeper sclerectomy is generally avoided for fear of

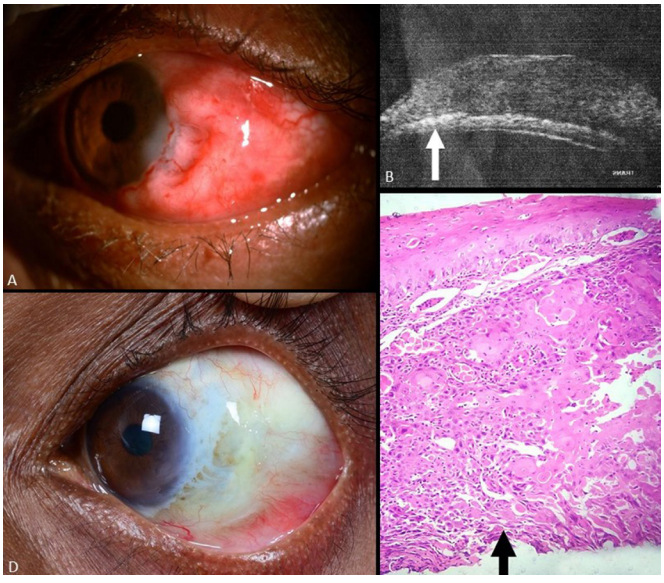

Figure 3 Left eye recurrent OSSN, (A). UBM showed corneal stromal invasion (white arrow), (B). Histopathology following excision biopsy confirmed the diagnosis of invasive squamous cell carcinoma with involvement of the corneal base (H&E, OMX100) (black arrow), (C). The patient is tumour-free at 2 years follow-up, (D). OSSN, ocular surface squamous neoplasia.

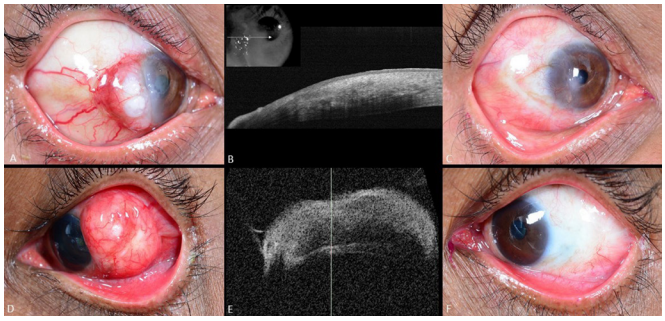

Figure 4 Right eye recurrent OSSN, (A), with corneal stromal and scleral invasion demonstrated on AS-OCT, (B). The patient was tumour-free at 20 months follow-up after tumour excision and Ru-106 plaque brachytherapy to the excision base, (C). Left eye nodular OSSN, (D), with scleral invasion on UBM, (E). The patient was tumour-free at 18 months follow-up after tumour excision and plaque brachytherapy to the excision base, (F). AS-OCT, anterior-segment optical coherence tomography; OSSN, ocular surface squamous neoplasia; Ru-106, ruthenium-106; UBM, ultrasound biomicroscopy.

scleral thinning, necrosis and inadvertent perforation, with possible intraocular tumour extension. In addition, deep sclerectomy may need reconstruction with an on-lay scleral patch graft for tectonic support, the use of which may preclude direct visualisation of the site of surgery and thus early clinical detection of local tumour recurrence. The utility of topical therapy is also limited in these eyes as the drugs do not penetrate the sclera,[1 15] and are relatively ineffective in invasive OSSN.[26 27]

For deeper scleral invasion in OSSN, radiotherapy has been known to achieve good success.[6–20] The plaque is sutured directly onto the ocular surface and the duration of the treatment calculated based on the radiation dose, thickness of the tumour and the type of radiation being used. In a report by Lommatzsch who treated 15 patients using strontium-90 (beta radiation) plaque brachytherapy, only 1 eye (7%) was noted to have a delayed recurrence at 5 years after the radiation therapy for which enucleation was necessary.[7] Of the 15 eyes, 11 eyes (73%) received radiation as a primary treatment after an incision biopsy was performed to confirm the diagnosis.[7]

Lecuona described 69 eyes with OSSN that underwent primary surgical excision without lamellar sclerectomy.[10] Histopathology of the specimen revealed either carcinoma in situ (n=28, 41%) or invasive squamous cell carcinoma (n=41, 59%).[10] Although the specimen were not analysed for excision base positivity, margin positivity was noted in 39 eyes (57%), and all patients received plaque radiotherapy with strontium-90 regardless of the histopathology result.[10] Recurrence was noted in eight eyes (11%), and the authors ascribed it to inadequate radiation coverage.[10] Cerezo *et al* and Kearsley *et al* also used strontium-90 as primary therapy in eyes with OSSN and obtained excellent results.[9 12] In all these series, the excision base positivity after surgical excision was not the consideration for the use of plaque radiotherapy.[9 10 12] Similarly, a study from Liverpool recommended the use of radiation in all cases of invasive OSSN irrespective of surgical clearance.[11] In their series, Ru-106 brachytherapy was used as a source of radiation and whenever the tumour location was inaccessible to plaque brachytherapy, proton beam radiotherapy was used.[11]

In contrast to the previous study, Arepalli *et al* described the use of plaque brachytherapy only in those eyes where histopathology confirmed excision base positivity (table 4).[15] In their case series consisting of 15 eyes with OSSN, all patients primarily underwent excision.[15] On histopathology, in addition to the

Table 4 Ru-106 plaque brachytherapy in OSSN with corneal stromal/scleral invasion: review of literature

Author	Year	No of cases	Prior surgical excision biopsy	Reason for plaque application	Type of plaque	Radiation dose	Margin	Follow-up duration	Recurrence at the same site	Enucleation/ exenteration	Complications
Ullman *et al*[13]	1995	1	Yes	Tumour recurrence	I-125	5660 cGy	NA	54 months	No	No	Dense posterior subcapsular cataract
Häberle *et al*[16]	1995	2	Yes	Tumour recurrence	Ru-106	100 Gy	NA	24 months	No	No	NA
Hwang *et al*[17]	2000	1	Yes	Tumour recurrence	I-125	6500 cGy	NA	17 months	Yes	Yes (Enucleation)	NA
Walsh-Conway and Conway[14]	2009	6	Yes	Scleral/corneal stromal surgical margin involvement	I-125	100 Gy	NA	Mean 23.4 months	No	No	Reduced vascularity, inflammation, corneal ulceration
Arepalli *et al*[15]	2014	15	Yes	Scleral/corneal stromal tumour base involvement	I-125	Mean 56 Gy	2 mm margin	41 months	No	Yes (enucleation=2, orbital exenteration=2)	Cataract, iris telangiectasia, corneal epithelial defect, corneal oedema, glaucoma
Lecuona *et al*[10]	2015	69	Yes	To prevent recurrence	Sr-90	60 Gy as 4 fractionated doses	NA	Median 27 months	6 eyes	No	Dry eye, astigmatism
Kenawy *et al*[11]	2015	14	Yes	To prevent recurrence in invasive squamous cell carcinoma	Ru-106	100 Gy	NA	Median <69 motnhs	Yes 1 eye had suspected persistent carcinoma in situ	No	None
Mittal *et al*[18]	2016	1	Yes	Scleral/corneal stromal tumour base involvement	Ru-106	5000 cGy	NA	24 months	No	No	No
Rospond-Kubiak *et al*[19]	2018	1	Yes	Residual intraocular tumour	Ru-106	86 Gy	NA	54 months	No	No	Sectoral cataract
Mendoza *et al*[20]	2018	1	Yes	Tumour recurrence	I-125	NA	NA	84 months	No	No	NA
Rao *et al* (current study)	2021	42	Yes	Scleral/corneal stromal tumour base involvement	Ru-106	5000 cGy	2 mm margin	Mean 36.9 months	No	No	Recurrent corneal epithelial defect

NA, not available; OSSN, ocular surface squamous neoplasia; Ru-106, ruthenium-106.

presence of deep scleral involvement in all 15 eyes, 3 eyes (20%) had tumour extension into the anterior chamber and Iodine-125 plaque brachytherapy was used to manage the residual tumour and intraocular extension.[15] Of the 15 eyes, 4 (27%) developed recurrence at a site remote from the area of irradiation, and the overall eye salvage rate was 67%.[15] The authors speculated that immunosuppression is an important underlying factor that could have led to remote progressive recurrence in these cases.[15]

It must be noted that in this series of 42 eyes, 39 eyes (93%) had scleral fixity clinically and scleral invasion on AS-OCT or UBM noted at the time of presentation. The utility of AS-OCT in judging scleral invasion is limited by keratin within the tumour (which causes a shadow artefact) and tumour thickness.[28] UBM may be more useful in the presence of keratin and for tumours up to 5 mm. A 3-Tesla MRI may be used to evaluate tumours >5 mm in thickness or in situations where the resolution of AS-OCT and/or UBM are suboptimal. The final decision to perform adjuvant plaque brachytherapy, however, is based on histopathology-confirmation of base positivity for invasive OSSN following excision biopsy.

On follow-up, 2 patients (5%) that developed tumour growth were noted to have hepatitis B infection. This growth was observed at a mean duration of 4 months postplaque treatment and at a site distant from the original tumour. This may be indicative of aggressive multifocal tumour in the background of immunosuppression that evolved over a period of time.

Ru-106 is a source of beta radiation and is known to have a theoretical heterogeneity in the dose emission.[29] However, the difference in the absorbed dose distribution is clinically not relevant if the lateral safety margin is ≥2 mm which was the margin used in all the cases in the series.[29] Ru-106, like strontium-90, provides a sharply cut-off, precise, low-penetration radiotherapy which is relatively safe to the deeper and surrounding normal tissue.[7–11] This results in fewer side effects as compared with Iodine-125 which is a source of gamma radiation.[13–15] Gamma radiation has a deeper penetrability and hence carries a greater chance for cataract and secondary glaucoma, especially when the radiation plaque is placed directly over the cornea, exposing the lens and angle structures to a higher dose of radiation.[13–15] While the most frequently reported symptoms with strontium-90 are dry eye and conjunctival telangiectasia, scleral thinning has also been reported.[10 12] In contrast, Ru-106 application in 14 eyes with OSSN did not lead to any complications as observed by Kenawy *et al*.[11] However, in a recent single case report of Ru-106 plaque brachytherapy for OSSN with corneal endothelial extension, the authors noted sectoral cataract formation at a 4-year follow-up.[19] In our series, we noted no major complications with the use of Ru-106 barring two eyes (5%) which developed recurrent corneal epithelial defect and were managed conservatively. None of the patients developed cataract or glaucoma at the final follow-up.

In conclusion, Ru-106 plaque brachytherapy achieves excellent tumour control in OSSN with corneal stromal and/or scleral invasion. Plaque brachytherapy in the management of OSSN must be guided by histopathology and is best used as an adjuvant therapy when the excision base is positive for invasive tumour.

Contributors All authors have participated in the assessment of the data and compilation of the manuscript. SGH accepts full responsibility for the work and/or the conduct of the study, had access to the data, and controlled the decision to publish.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval Informed patient consent and institutional review board approval were obtained. The study conformed to the tenets of the Declaration of Helsinki.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as online supplemental information. NA.

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