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Proton beam radiotherapy of locally advanced or recurrent conjunctival squamous cell carcinoma: experience of the CATANA Centre

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Abstract

Aim: Conjunctival squamous cell carcinoma (SCC) is a rare tumour of the ocular region and microscopic radical surgical is difficult. There are no single guidelines for therapeutic management and the role of radiation therapy is not clearly defined although conventionally photon or electron beams are used. Proton beam radiotherapy (PBRT) is a new option for a conservative approach and allows good sparing of the organs at risk.
Materials and methods: After surgical resection, we collected 15 cases treated at our institution with PBRT. The dose delivered was between 48 and 60 Gy relative biological effectiveness (RBE), with fractions of 12–15 Gy RBE.
Results: After an average period of 48 months, the patients achieved excellent disease control (overall survival and disease-free survival: 86·6%), with minimal acute and late toxicity.
Findings: In this work, we present our experience on the use of PBRT technique in SCC treatment. A larger sample of patients is needed to draw conclusions about the impact of this treatment on disease recurrence and overall survival.

Introduction

Squamous conjunctival carcinoma typically occurs on the bulbar conjunctiva, rising at the limbus and often diffuses onto the cornea.[1] The risk factors are exposure to solar ultraviolet (UV) radiation outdoors, human immunodeficiency virus (HIV)/acquisition immunodeficiency syndrome (AIDS), human papillomavirus (HPV), syndromes of immune dysregulation, race, male gender, allergic conjunctivitis, cigarette smoking and other predisposing factors.[2–12]

Worldwide, conjunctival squamous cell carcinoma (SCC) is an uncommon disease, the incidence of which varies geographically from 0·03 to 1·9 per 100,000/year in the Caucasian population,[2,6] and from 3 to 3·4 per 100,000/year in African ethnicity populations.[7]

Even before the term ocular superficial squamous neoplasia (OSSN) was introduced, to understand the spectrum of conjunctival and corneal intraepithelial neoplasia and SCC,[3] published series frequently included intraepithelial and invasive squamous tumours.[4] In general, the SCC of the conjunctiva is regarded as a low-grade malignancy.

The main risk factor for OSSN is UV B radiation, with people chronically exposed to direct solar light and those involved in outdoor occupations being at the most risk.[5] According to an Australian population-based study, individuals with fair skin, light iris colour and/or liable to sunburn, those who spent >50% of the time outdoors during the first 6 years of life and those living within 30 km of the equator have the greatest risk of developing the tumour.[6]

Conjunctival SCC has also been associated with HPV infection, especially genotype 16.[8,9] The human immunodeficiency viruses (HIVs have been correlated with an eight times greater risk of OSSN, with the highest incidence rate in the first 2 years of AIDS.[10,11]

Syndromes of immune dysregulation including non-Hodgkin's lymphoma, iatrogenic transplantation of post-organ immunosuppression, pigmentary xeroderma, asthma/eczema/atopic diseases, ocular cicatricial pemphigus and the Papillon–Lefevre syndrome can also make individuals susceptible to OSSN.[12]

The SCC has a variable clinical presentation.[13,14] Usually, it is a unilateral vascularised limbar mass located in the inter-palpebral fissure.[3]

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The management of OSSN includes surgical resection, topical chemotherapy [Mitomycin C (MMC), 5-Fluorouracil (5-FU)], topical/local immunomodulation with interferon-alpha-2b (IFN-a2b), topical antiviral medications (Cidofovir), photodynamic therapy, cryotherapy[12] and radiotherapy [external beam radiotherapy (EBRT), proton beam radiotherapy (PBRT) and Strontium-90 or Ruthenium-106 plaque brachytherapy][15–18] to control residual microscopic tumour following surgical resection, as a primary treatment or to treat recurrent disease.

Due to the prevailing locoregional diffusion of the SCC, PBRT is a valid alternative to surgical treatments (enucleation or exenteration) and other conservative treatments. The dose distribution of protons makes them very effective for treating small volumes at high doses and almost completely sparing neighbouring tissues, compared to photon-beam radiotherapy. The conservative treatment also increases patients' quality of life.

The side effects of PBRT are rare but can include dry eye syndrome, red-eye, keratinisation of the conjunctiva, trichiasis, blepharitis, radiation retinopathy, cataract, keratopathy, lacrimal duct stenosis and corneal perforation.

The purpose of this study was to undertake a retrospective review of patients who had been treated for SCC at our centre using PBRT, to review overall treatment outcomes. Data were collected from 15 SCC patients with gross residual disease after surgery or who were not candidates for surgical excision.

Materials and Methods

From 2010 to 2019, we treated 15 patients with conjunctival SCC using PBRT. Records of all patients treated during this period were included in the study and retrospectively analysed (Table 1). The patients were predominantly male (11 M/4 F). The age of the patients at the time of treatment was between 31 and 87 years. Only one patient was infected with HIV. Almost all patients had low-grade malignant lesions (G1–2). Only two patients had high-grade malignant lesions (G3).

Clinical appearance at presentation was documented for all patients. Two of the 15 patients presenting with a mass also had altered or decreased vision. Seven presented with irritation or redness. One patient with diffuse disease presented as recurrent conjunctivitis (Figure 1). One patient presented with an ulcerated lesion.

All patients underwent staging investigation with an MRI of the ocular-orbital region, CT scan of neck and thorax (Figure 2a–c) and an eye examination.

Two patients received induction chemotherapy before PBRT, one with a Cisplatin-5-FU schedule and the other with a TPF (Docetaxel, Cisplatin and 5-FU) schedule. One patient underwent chemotherapy after disease recurrence with Carboplatin-5-FU schedule. The median follow-up period was 48 months.

After obtaining an informed consent from the patients and their relatives, radiotherapy was proposed. PBRT was delivered at CATANA (Centro di AdroTerapia ed Applicazioni Nucleari Avanzate) Centre at INFN-LNS (Istituto Nazionale di Fisica Nucleare-Laboratori del Sud) of Catania. The accelerator in use is a Super-conducting Cyclotron that delivers a proton beam at an energy of 62 MeV with an intensity of 10–20 Na. A dedicated beamline is produced to bring the proton beam directly to the eye of the patients, who are placed in a seated position on a treatment chair.

Patient immobilisation is achieved by the use of a thermoplastic mask fixed on a frame and a bite-block (Figure 3). Dose distribution follows the well-known Bragg-peak phenomenon. This phenomenon is responsible for an increased dose deposition as the particles travel through the tissue, with a constant low entry dose, producing a region of high dose at a depth determined by the initial proton energy, and no dose beyond the end of the range. For a 62 MeV proton beam, the width of the fall-off of the dose from 90 to 10% is about 1 mm at a depth of 3 cm.

The target volume includes the whole lesion with a 3-mm margin around it. The dose profile is represented in Figure 4. Treatment plans showed no dose deposition to the lens, lacrimal gland and other orbital tissues. The eyelids were placed outside of the treatment field by using an adhesive patch to retract the eyelids. A customised brass collimator is used to shape the proton beam to cover the entire lesion in the treatment field. Patients are asked to fix on a small red dot in the space delineated by a laser light to create an optimal beam angle, this is in order to avoid unnecessary irradiation to organs at risk, and to produce a gaze angle to treat the tumour, while sparing as much as possible of the cornea, pupil and iris. During the proton therapy the patient's eye is monitored by a video camera, the position of the pupil marked on the display so that the tiniest movements can be immediately detected and irradiation can be suspended. The treatment is carried out in four fractions on four consecutive days. The prescribed total dose was between 48 and 60 Gy RBE (relative biological effectiveness) with a fraction of 12–15 Gy RBE. (Table 1)

Treatment procedures are almost the same as those used in the treatment of other more frequent ocular (i.e., uveal melanoma) or orbital and periorbital tumours (i.e., lymphoma, porocarcinoma of sweat gland and basal cell carcinoma) at CATANA Centre.[19–21]

Results

In this study, after the treatment of 15 patients with SCC and treated with PBRT, excellent results were achieved in overall survival, disease-free survival and treatment tolerance. The treatment was well tolerated by all the patients. No patient had to stop treatment due to acute toxicity: conjunctivitis, keratitis or blepharitis rapidly regressed with topical or systemic administration of corticosteroids. Late toxicities have been minimal. One patient showed lacrimal duct stenosis, severe conjunctivitis and red-eye syndrome that have regressed after a few months. One patient presented with a lacrimal duct stenosis and had to undergo surgery to unlock the tear canal (Figure 7). One patient had severe eyelid perforation to the inner canthus of the eye. After a median follow-up of 48 months, an overall survival (OS) rate of 86·6% is reported and two patients died from causes not related to the disease. In addition, only two patients had a local disease recurrence (Disease-free survival 86·6%).

Discussion

The SCC has a variable clinical presentation and evolution. Photophobia, red-eye, irritation, foreign body sensation and a white, painless, progressive growth on the surface of the eye are common presenting symptoms. Most tumours take place in the interpalpebral fissure, especially on the nasal side.[13,14] They involve the conjunctiva and may expand onto the peripheral cornea, so visual acuteness is frequently normal in the early stages. It usually involves only one eye. The surface may be gelatinous, papillomatous or fibrovascular. There is usually inflammation, leucoplakia and markedly dilated blood vessels, referred to as feeder vessels.

The therapeutic approach of this disease can be varied: surgery resection, topical chemotherapy (MMC or 5-FU), photodynamic treatment, immunomodulation with interferon[12] and radiotherapy (PBRT, EBRT or brachytherapy).

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Table 1. Characteristics of patients and treatments

Patients	Gender	Year of treatment	Age at PBRT	Dose Gy RBE	Grading	FU interval (months)	Recurrence/metastasis	Status	CHT	Late toxicity	HIV/HPV
B.U.	M	2010	77	50	2	52	No	Alive	–	–	–
U.G.	F	2010	76	60	2	39	No	Deceased	–	–	–
M.V.	M	2011	81	60	1	54	No	Alive	–	–	–
B.L.	F	2011	72	50	2	60	No	Alive	–	Eyelid oedema	–
P.P.	M	2011	63	48	2	88	No	Alive	–	–	–
I.T.	M	2011	61	48	2	65	No	Alive	–	–	–
G.G.	M	2012	54	48	2	47	Local recurrence	Alive	TPF	–	–
E.D.	M	2012	74	48	3	78	Local recurrence	Alive	Carbo/5-FU	Cataract	–
G.E.	F	2015	31	52	2	66	No	Alive	–	–	HIV
B.M.	F	2016	81	52	2	84	No	Alive	–	Conjunctivitis	–
M.G.	M	2018	85	60	3	24	Controlateral corner recurrence	Deceased	–	–	–
C.S.	M	2018	46	60	2	22	No	Alive	Cis/5-FU	Conjunctivitis, red-eye Lacrimal duct stenosis	–
T.R.	M	2018	87	60	2	19	Controlateral corner recurrence	Alive	–	Eyelid perforation	–
M.S.	M	2019	58	60	2	12	No	Alive	–	Lacrimal duct stenosis	–
G.G.	M	2019	83	60	2	10	No	Alive	–	–	–

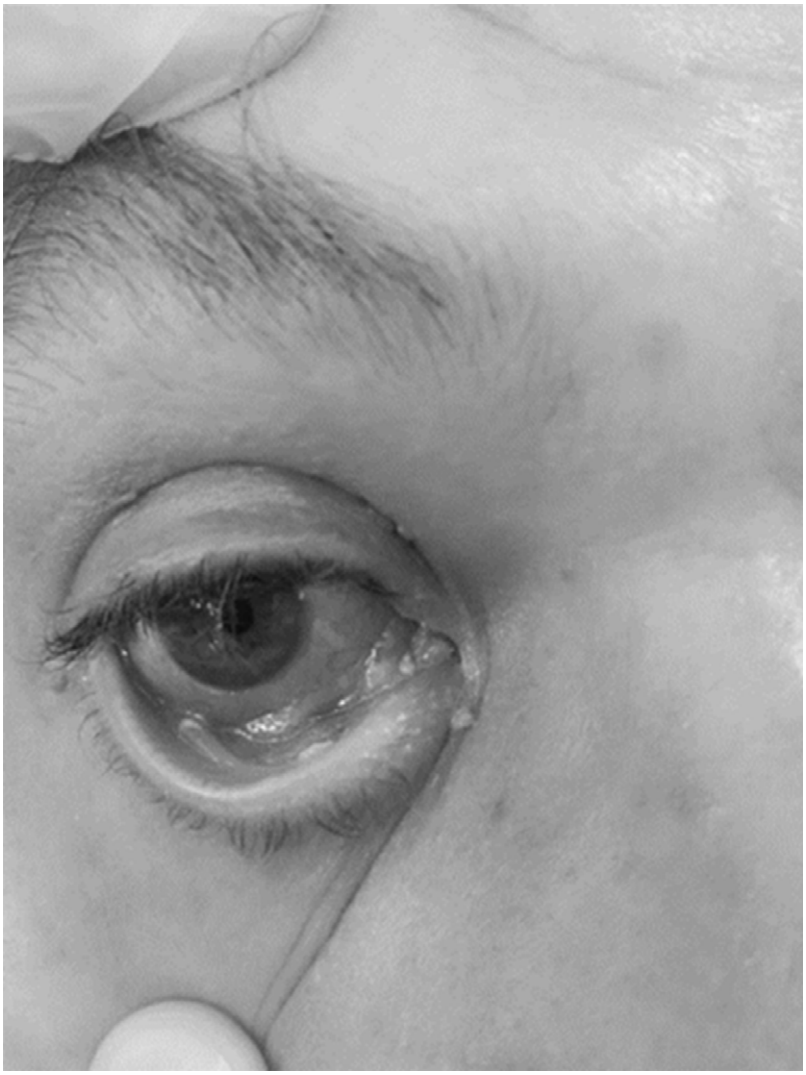

Figure 1. SCC clinical presentation.

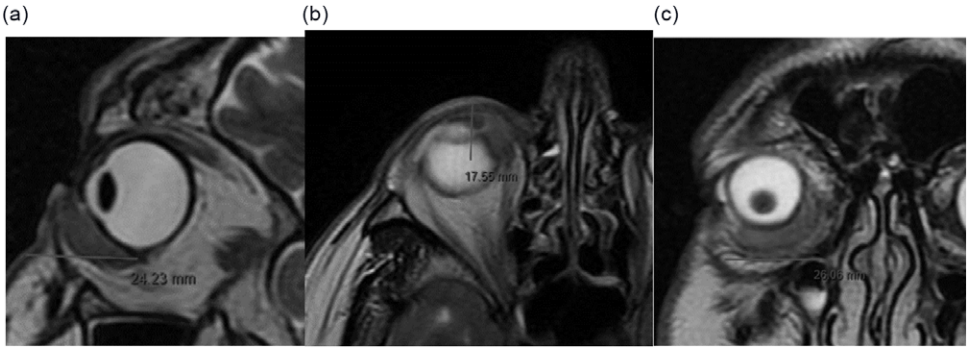

Figure 2. (a–c) MRI images show the localisation of the disease.

In our centre, we have treated 15 SCC patients with PBRT with a median follow-up of 48 months. Currently, 13 patients are alive (OS 86·6%) and 2 patients died from causes not related to the disease. We have seen a complete response in 13 out of 15 patients: only 2 patients had a local recurrence of disease (DFS 86·6%) and were treated later with surgery. In six patients the late side effects have regressed and one patient presented with severe late radio-induced toxicity that regressed after a few months: grade III conjunctivitis, red-eye syndrome and lacrimal duct stenosis (Figure 5). For the same patient, MRI images show a complete resolution of the disease (Figure 6). One patient presented with a lacrimal duct stenosis and had to undergo surgery to unblock the tear canal (Figure 7). One patient had severe eyelid perforation to the inner canthus of the eye.

Surgical excision is the gold standard treatment according to current evidence. In the review by Cicinelli et al.,[12] authors describe how the surgical removal of a conjunctival lesion is performed as specified by Shields' 'no touch' technique to prevent the potential risk of seeding and having large macroscopically tumour-free margins (at least 4 mm).

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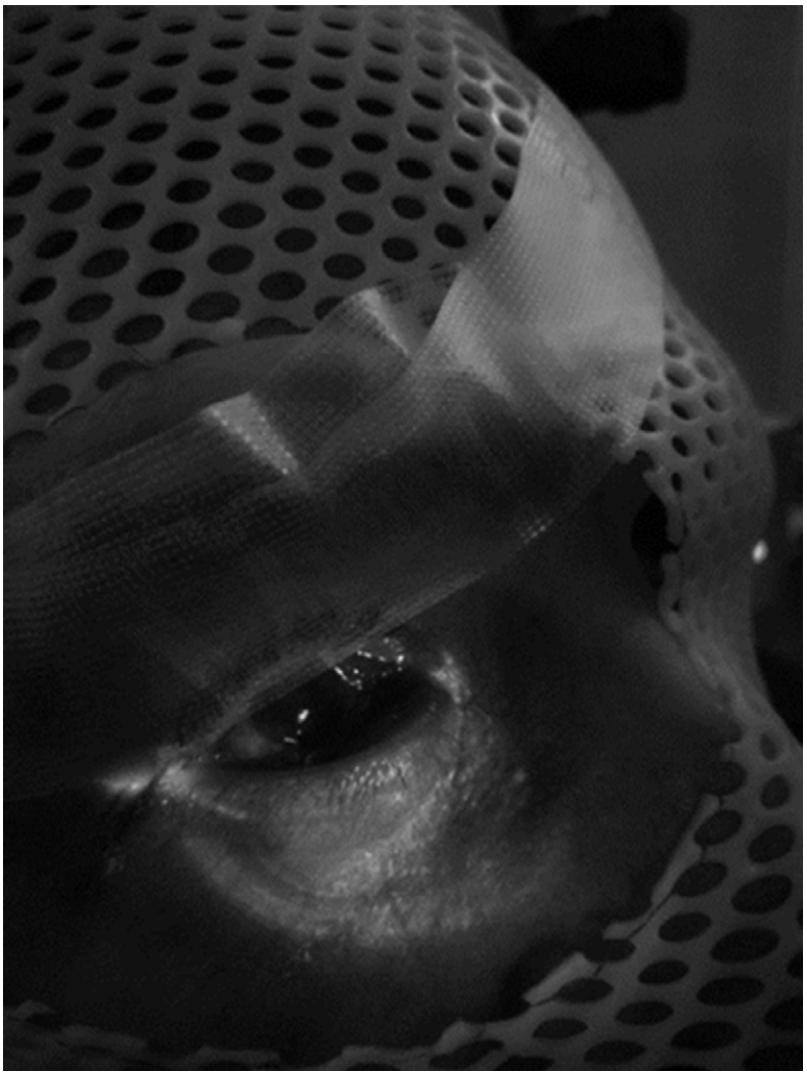

Figure 3. Positioning of the patient with a thermoplastic mask and rising of the eyelids.

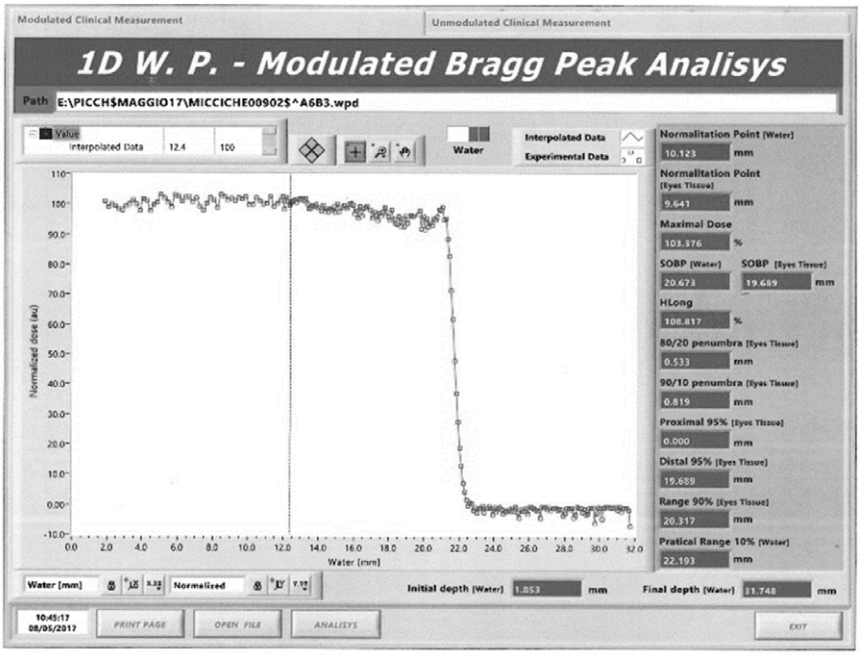

Figure 4. Proton beam dose profile showing the rapid dose fall-off at the desired depth (modulated Bragg peak).

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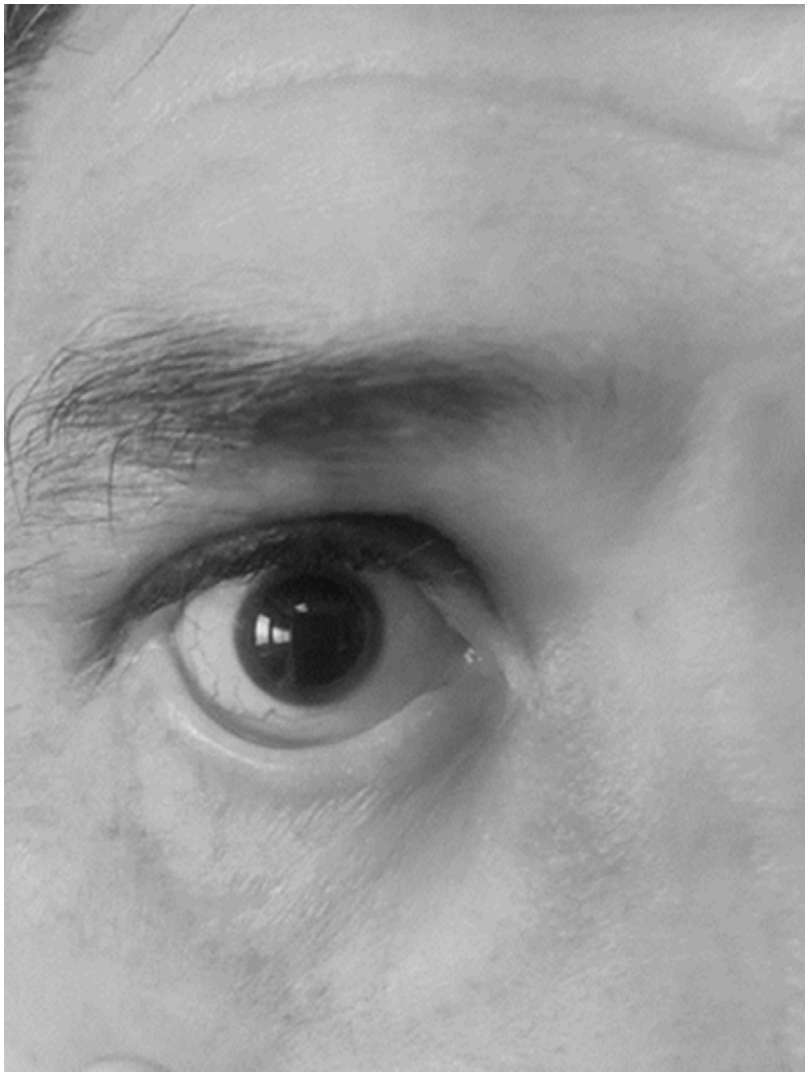

Figure 5. Patient with complete *restitutio ad integrum,* after grade III conjunctivitis, red-eye syndrome and lacrimal duct stenosis.

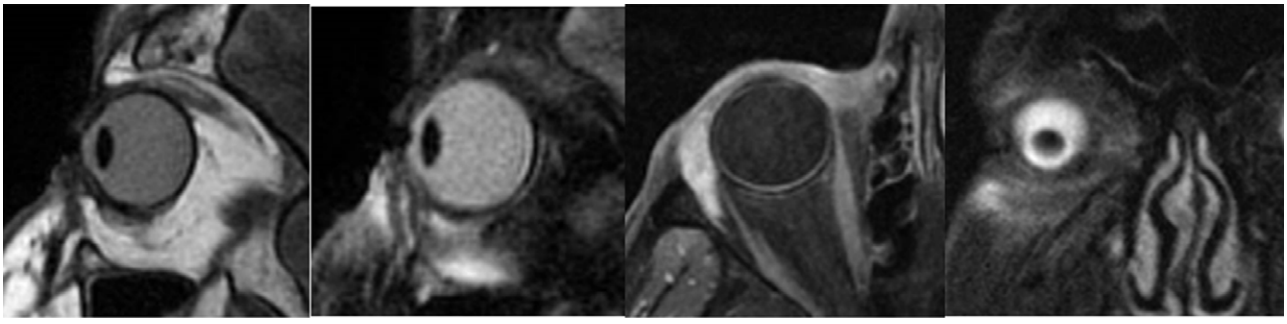

Figure 6. MRI images show the complete resolution of the disease.

Ghicuni et al.[22] describe the adjuvant treatments to improve surgical radicality including cryotherapy, where 2–4 freeze–thaw cycles are used to erase residual tumour at the bed and clear margins. In addition, the topical application of cytotoxic drugs, such as 5-FU and Mitomycin C, can be applied to the tumour bed for about 2.5 min then washed out. Other agents include IFN-a2b drops, all-trans retinoic acid, anti-VEGF agents, Cyclosporin A and radiotherapy.

Several radiotherapy methods have been used for post-operative treatment or for local recurrence. Belaïd et al.[17] treated 24 patients with post-operative radiation therapy. Eighteen patients were treated with kilovoltage radiation therapy (KVRT). The average delivered dose to the tumour bed was 64 Gy. Two patients were treated with Strontium 90 plaque brachytherapy (two fractions of 17 Gy). Four patients were treated with a combination of KVRT and Strontium 90 plaque brachytherapy. After a median follow-up of 110 months,

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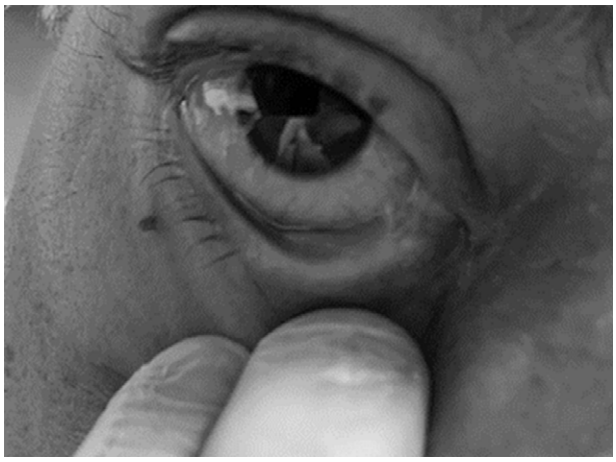

Figure 7. Inner canthus fibrosis with lacrimal duct stenosis.

19 patients were alive and 17 patients with no evidence of local recurrence. Two patients had a local recurrence and were referred for surgery. Two patients were lost to follow-up. Three patients died without evidence of a relapse. They reported that the 5-year relapse-free survival rate was 90·9% and the 5-year OS was 86·4%. The reported toxicity was cataract in 15 patients, conjunctivitis in 17 patients, tearing of cornea in 13 patients and glaucoma in 2 patients.

Graufe et al.[23] treated eight patients with local SCC recurrence with electron beams. Two patients were HIV positive. The dose range was from 50 to 60 Gy in 2·0- to 2·5-Gy daily fractions. After a mean 30·25 month of 5-FU, they found 75% local disease control. Only two patients developed a tumour recurrence. They reported side effects as mild-to-moderate erythema in seven patients and severe in one patient, one case of keratitis, a case of secondary of trichiasis and three patients with persistent madarosis as side effects.

In a major review, Finger discussed the role of EBRT with the intensity modulated method (IMRT) in the treatment of SCC.[24] Modern radiotherapy techniques can be used to irradiate tumour, in cases not eligible for surgery, with better sparing of the surrounding healthy tissues, as accepted for other oncological indications.[25,26] The dose range used varied from 34 to 65 Gy, with an average dose of 50 Gy.[24]

Although the literature on SCC is scarce and in many publications they are case reports, they have shown that SCC can be treated with radical PBRT with excellent results in terms of OS, disease-free survival and toxicity[15,16] and it can be a valid alternative to orbit exenteration or enucleation.

Ramonas et al.[15] treated a 91-year-old patient with a moderate-to-well-differentiated SCC of the conjunctiva with intraocular invasion with radical PBRT as an alternative to enucleation. Slit-lamp examination disclosed a highly vascularised conjunctival amelanotic mass arising from the limbus and extending onto the cornea from the 1 o'clock to 5:30 meridian in the right eye. Ultrasound biomicroscopy described and confirmed the invasion of the conjunctival lesion into the anterior chamber angle from the 1 o'clock to 5:30 position. The dose used for treatment was 32 Gy (8 Gy divided over four treatments on four consecutive days). After 9 months of follow-up, there was no sign of disease recovery and the regression was stable.

El-Assal et al.[16] treated two elderly patients (73 and 83 years) with OSSN with radical PBRT after excisional biopsy. Four cycles of topical Mytomycin C were administered to one patient. The dispensed dose was 53·1 Gy in four fractions on four consecutive days for both patients. The patients remain recurrence free at follow-up.

In a French ocular oncologic centre, Caujolle et al.[18] treated 15 patients using PBRT either for recurrent or incompletely resected tumours with positive margins for conjunctival SCC. The doses delivered to the target volume varied from 40 to 60 Gy. After a median follow-up of 39·1 months, the tumour control rate was up to 86·8% with acceptable side effects.

In the present study, the data have shown PBRT to also be an effective and safe conservative treatment of SCC which can have a real and psychological advantage in terms of the patient quality of life. PBRT provides good disease control and patients demonstrated few side effects of treatment.

Due to the rarity of the disease, a limitation of this study is the small number of patients available to be treated to provide data for analysis for this study. Future studies need to include larger cohorts of patients so that there will be more data to evaluate the real advantage of proton therapy over other therapeutic methods.

Conclusion

This study suggests proton beam therapy as a good alternative to surgical excision or enucleation. PBRT has been shown to be effective and safe in the conservative treatment of squamous cell conjunctival carcinoma, thanks to the better dose distribution compared to the other radiotherapy methods. This conservative approach also has a real and psychological advantage in terms of patient's quality of life.

Data from this study show that post-excisional PBRT for the treatment of patients with SCC is a treatment that allows good disease control with few side effects.

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Conflicts of Interest. None.

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